

N2-(3-ethoxycarbonylmethyleneaminophenyl)-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine and N-methylpiperazine were reacted to prepare N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-(N-methyl)piperazino)carbonylmethyleneaminophenyl]-2,4-pyrimidinediamine. LCMS: ret. time: 15.75 min.; purity: 99.1%; MS (m/e): 494.06 (MH⁺).

7.3.574 N4-(3,4-Ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-2-hydroxyethyleneamino)carbonylmethyleneaminophenyl]-5-fluoro-2,4-pyrimidinediamine (R950195)

In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-morpholinoethyleneamino)carbonylmethyleneaminophenyl]-2,4-pyrimidinediamine, N2-(3-ethoxycarbonylmethyleneaminophenyl)-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine and 2-aminoethanol were reacted to prepare N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-2-hydroxyethyleneamino)carbonylmethyleneaminophenyl]-5-fluoro-2,4-pyrimidinediamine. LCMS: ret. time: 16.23 min.; purity: 97.3%; MS (m/e): 455.02 (MH⁺).

7.3.575 N4-(3,4-Ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)ethyleneaminocarbonylmethyleneaminophenyl]-2,4-pyrimidinediamine (R950196)

In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-morpholinoethyleneamino)carbonylmethyleneaminophenyl]-2,4-pyrimidinediamine, N2-(3-ethoxycarbonylmethyleneaminophenyl)-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine and N-methyl-ethylen-1,2-diamine were reacted to prepare N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)ethyleneaminocarbonylmethyleneaminophenyl]-2,4-pyrimidinediamine. LCMS: ret. time: 15.34 min.; purity: 98.2%; MS (m/e): 468.06 (MH⁺).

7.3.576 N4-(3,4-Ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-piperazino)carbonylmethyleneaminophenyl]-5-fluoro-2,4-pyrimidinediamine (R950197)

In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-morpholinoethyleneamino)carbonylmethyleneaminophenyl]-2,4-pyrimidinediamine, N2-(3-ethoxycarbonylmethyleneaminophenyl)-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine and piperazine were reacted to prepare N4-(3,4-ethylenedioxyphenyl)-5-

fluoro-N2-[3-(N-piperazino)carbonylmethyleneaminophenyl]-5-fluoro-2,4-pyrimidinediamine. LCMS: ret. time: 15.38 min.; purity: 93.2%; MS (m/e): 479.99 (MH⁺).

7.3.577 N2-[3-(N-Benzylamino)ethyleneaminocarbonylmethyleneaminophenyl]-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R950198)

In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-morpholinoethyleneamino)carbonylmethyleneaminophenyl]-2,4-pyrimidinediamine, N2-(3-ethoxycarbonylmethyleneaminophenyl)-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine and N-benzyl-ethylen-1,2-diamine were reacted to prepare N2-[3-(N-benzylamino)ethyleneaminocarbonylmethyleneaminophenyl]-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine. LCMS: ret. time: 17.70 min.; purity: 92.5%; MS (m/e): 544.04 (MH⁺).

7.3.578 N2-[3-(N,N'-Bis(2-N-hydroxyethyl)amino)carbonylmethyleneaminophenyl]-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R950199)

In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-morpholinoethyleneamino)carbonylmethyleneaminophenyl]-2,4-pyrimidinediamine, N2-(3-ethoxycarbonylmethyleneaminophenyl)-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine and N,N'-bis(2-hydroxyethylene)amine were reacted to N2-[3-(N,N'-bis(2-N-hydroxyethyl)amino)carbonylmethyleneaminophenyl]-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine. LCMS: ret. time: 15.81 min.; purity: 99.4%; MS (m/e): 499.01 (MH⁺).

7.3.579 5-Fluoro-N4-(3-hydroxyphenyl)-N2-[3-(N-methylamino)carbonylmethyleneaminophenyl]-2,4-pyrimidinediamine (R950217)

In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-morpholinoethyleneamino)carbonylmethyleneaminophenyl]-2,4-pyrimidinediamine, N2-(3-ethoxycarbonylmethyleneaminophenyl)-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine and methylamine were reacted to prepare 5-fluoro-N4-(3-hydroxyphenyl)-N2-[3-(N-methylamino)carbonylmethyleneaminophenyl]-2,4-pyrimidinediamine. LCMS: ret. time: 14.41 min.; purity: 93.0%; MS (m/e): 383.02 (MH⁺).

7.3.580 N2-(3-Aminocarbonylmethyleneaminophenyl)-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine (R950219)

In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-morpholinoethyleneamino)carbonylmethyleneaminophenyl]-2,4-pyrimidinediamine, N2-(3-ethoxycarbonylmethyleneaminophenyl)-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine and aqueous ammonia were reacted to prepare N2-(3-aminocarbonylmethyleneaminophenyl)-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine. LCMS: ret. time: 14.23 min.; purity: 95.0%; MS (m/e): 369.03 (MH⁺).

7.3.581 N2-[3-(N,N-Dimethylamino)carbonylmethyleneaminophenyl]-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine (R950220)

In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-morpholinoethyleneamino)carbonylmethyleneaminophenyl]-2,4-pyrimidinediamine, N2-(3-ethoxycarbonylmethyleneaminophenyl)-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine and dimethylamine were reacted to prepare N2-[3-(N,N-dimethylamino)carbonylmethyleneaminophenyl]-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine. LCMS: ret. time: 16.59 min.; purity: 96.5%; MS (m/e): 397.06 (MH⁺).

7.3.582 5-Fluoro-N4-(3-hydroxyphenyl)-N2-[3-(N-morpholino)carbonylmethyleneaminophenyl]-2,4-pyrimidinediamine (R950221)

In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-morpholinoethyleneamino)carbonylmethyleneaminophenyl]-2,4-pyrimidinediamine, N2-(3-ethoxycarbonylmethyleneaminophenyl)-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine and morpholine were reacted to prepare 5-fluoro-N4-(3-hydroxyphenyl)-N2-[3-(N-morpholino)carbonylmethyleneaminophenyl]-2,4-pyrimidinediamine. LCMS: ret. time: 16.29 min.; purity: 91.5%; MS (m/e): 439.03 (MH⁺).

7.3.583 5-Fluoro-N4-(3-hydroxyphenyl)-N2-[3-(N-piperazino)carbonylmethyleneaminophenyl]-2,4-pyrimidinediamine (R950222)

In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-morpholinoethyleneamino)carbonylmethyleneaminophenyl]-2,4-pyrimidinediamine, N2-(3-ethoxycarbonylmethyleneaminophenyl)-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine and piperazine were reacted to prepare 5-fluoro-N4-(3-hydroxyphenyl)-

N2-[3-(N-piperazino)carbonylmethyleneaminophenyl]-2,4-pyrimidinediamine. LCMS: ret. time: 13.04 min.; purity: 89.9%; MS (m/e): 438.06 (MH⁺).

7.3.584 5-Fluoro-N4-(3-hydroxyphenyl)-N2-[3-[N-(N-methyl)piperazino]carbonylmethyleneaminophenyl]-2,4-pyrimidinediamine (R950223)

In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-morpholinoethyleneamino)carbonylmethyleneaminophenyl]-2,4-pyrimidinediamine, N2-(3-ethoxycarbonylmethyleneaminophenyl)-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine and N-methylpiperazine were reacted to prepare 5-fluoro-N4-(3-hydroxyphenyl)-N2-[3-[N-(N-methyl)piperazino]carbonylmethyleneaminophenyl]-2,4-pyrimidinediamine. LCMS: ret. time: 12.06 min.; purity: 98.7%; MS (m/e): 452.06 (MH⁺).

7.3.585 5-Fluoro-N4-(3-hydroxyphenyl)-N2-[3-(N-2-hydroxyethylamino)carbonylmethyleneaminophenyl]-2,4-pyrimidinediamine (R950224)

In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-morpholinoethyleneamino)carbonylmethyleneaminophenyl]-2,4-pyrimidinediamine, N2-(3-ethoxycarbonylmethyleneaminophenyl)-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine and 2-aminoethanol were reacted to prepare 5-fluoro-N4-(3-hydroxyphenyl)-N2-[3-(N-2-hydroxyethylamino)carbonylmethyleneaminophenyl]-2,4-pyrimidinediamine. LCMS: ret. time: 13.28 min.; purity: 97.3%; MS (m/e): 413.04 (MH⁺).

7.3.586 5-Fluoro-N4-(3-hydroxyphenyl)-N2-[3-[(N-methylamino)ethylamino]carbonylmethyleneaminophenyl]-2,4-pyrimidinediamine (R950225)

In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-morpholinoethyleneamino)carbonylmethyleneaminophenyl]-2,4-pyrimidinediamine, N2-(3-ethoxycarbonylmethyleneaminophenyl)-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine and N-methyl-ethylen-1,2-diamine were reacted to prepare 5-fluoro-N4-(3-hydroxyphenyl)-N2-[3-[(N-methylamino)ethylamino]carbonylmethyleneaminophenyl]-2,4-pyrimidinediamine. LCMS: ret. time: 12.31 min.; purity: 94.7%; MS (m/e): 426.01 (MH⁺).

7.3.587 5-Fluoro-N4-(3-hydroxyphenyl)-N2-[3-[(N-2-morpholinoethylamino)carbonylmethyleneaminophenyl]-2,4-pyrimidinediamine (R950226)

In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-morpholinoethyleneamino)carbonylmethyleneaminophenyl]-2,4-pyrimidinediamine, N2-(3-ethoxycarbonylmethyleneaminophenyl)-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine and N-morpholinylethylamine were reacted to prepare 5-fluoro-N4-(3-hydroxyphenyl)-N2-[3-(N-2-morpholinoethylamino)carbonylmethyleneaminophenyl]-2,4-pyrimidinediamine. LCMS: ret. time: 12.66 min.; MS (*m/e*): 482.39 (MH⁺).

7.3.588 R935184: 5-Fluoro-N2-[4-(N-methylamino)carbonylmethyleneoxyphenyl]-N4-(3,4-propylenedioxyphenyl)-2,4-pyrimidinediamine

In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, 5-fluoro-N2-[4-(methoxycarbonylmethyleneoxy)phenyl]-N4-(3,4-propylenedioxyphenyl)-2,4-pyrimidinediamine was reacted with Me₂NH.HCl and *i*-Pr₂NEt in methanol to produce 5-fluoro-N2-[4-(N-methylamino)carbonylmethyleneoxyphenyl]-N4-(3,4-propylenedioxyphenyl)-2,4-pyrimidinediamine. LCMS: ret. time: 6.91 min.; purity: 98%; MS (*m/e*): 440 (MH⁺).

7.3.589 R935196: N2-[3-(1-Bis(N-methylaminocarbonyl)ethoxy)phenyl]-5-fluoro-N4-(4-isopropoxyphenyl)-2,4-pyrimidineamine:

In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, N4-[3-(1-bis(ethyloxycarbonyl)ethoxy)phenyl]-5-fluoro-N2-[4-isopropoxyphenyl]-2,4-pyrimidinediamine was reacted with Me₂NH.HCl and *i*-Pr₂NEt in presence of methanol to produce N2-[3-(1-bis(N-methylaminocarbonyl)ethoxy)phenyl]-5-fluoro-N4-(4-isopropoxyphenyl)-2,4-pyrimidineamine. ¹H NMR (DMSO-d₆): δ 9.18 (s, 1H), 9.15 (s, 1H), 8.07 (app qt, 2H, J= 4.7 Hz), 8.01 (d, 1H, J= 3.5 Hz), 7.65-7.62 (m 2H), 7.36 (br s, 1H), 7.28 (dd, 1H, J= 1.1 and 8.2 Hz), 7.03 (t, 1H, J= 8.2 Hz), 6.87 (d, 2H, J= 8.8 Hz), 6.35 (dd, 1H, J= 1.1 and 8.8 Hz), 4.54 (q, 1H, J= 6.4 Hz), 2.62 (d, 6H, J= 4.7 Hz), 1.49 (s, 3H), 1.23 (d, 6H, J= 5.8 Hz). LCMS: ret. time: 19.40 min.; purity: 94%; MS (*m/e*): 497 (MH⁺).

7.3.590 R935202: 5-Fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-N4-(3,4-propylenedioxyphenyl)-2,4-pyrimidinediamine:

In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, 5-fluoro-N2-[3-(methoxycarbonylmethyleneoxy)phenyl]-N4-(3,4-propylenedioxyphenyl)-2,4-pyrimidinediamine was reacted with Me₂NH.HCl to give 5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-N4-(3,4-propylenedioxyphenyl)-2,4-pyrimidinediamine. ¹H NMR (DMSO-d₆): δ 9.21 (s, 1H), 9.19 (s, 1H), 8.06 (d, 1H, J= 4.1 Hz), 7.94 (q, 1H, J= 3.5 Hz), 7.42-7.38 (m, 2H), 7.30 (d, 2H, J= 7.6 Hz), 7.12 (t, 1H, J= 7.6 Hz), 6.89 (d, 1H, J= 8.2 Hz), 6.47 (dd, 1H, J= 2.3 and 8.8 Hz), 4.33 (s, 2H), 4.11-4.03 (m, 4H), 2.63 (d, 3H, J= 4.7 Hz), 2.08-2.03 (m, 2H). LCMS: ret. time: 17.33 min.; purity: 98%; MS (m/e): 440 (MH⁺).

7.3.591 R935206: N2, N4-Bis[1-(N-methylaminocarbonyl)methyl-indazoline-6-yl]-5-fluoro-2,4-pyrimidinediamine

In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, N2, N4-Bis[1-(methoxycarbonyl)methyl-indazoline-6-yl]-5-fluoro-2,4-pyrimidinediamine and was reacted with Me₂NH.HCl and *i*-PrN₂Et in presence of methanol to produce N2, N4-bis[1-(N-methylaminocarbonyl)methyl-indazoline-6-yl]-5-fluoro-2,4-pyrimidinediamine. ¹H NMR (DMSO-d₆): δ 9.56 (s, 1H), 9.40 (s, 1H), 8.17 (d, 1H, J= 3.5 Hz), 8.12 (s, 1H), 7.99 (s, 1H), 7.96 (s, 2H), 7.90 (s, 2H), 7.66 (d, 1H, J= 8.8 Hz), 7.56 (d, 1H, J= 8.8 Hz), 7.49 (dd, 1H, J= 1.7 and 8.8 Hz), 7.34 (dd, 1H, J= 1.7 and 8.8 Hz), 4.90 (s, 2H), 4.66 (s, 2H), 2.56 (d, 6H, J= 4.11 Hz). LCMS: ret. time: 13.85 min.; purity: 98%; MS (m/e): 503 (MH⁺).

7.3.592 R935212: N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[1-(N-methylaminocarbonyl)methyl-indazoline-6-yl]-2,4-pyrimidinediamine

In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[1-(methoxycarbonyl)methyl-indazoline-6-yl]-2,4-pyrimidinediamine and Me₂NH.HCl was reacted to produce N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[1-(N-methylaminocarbonyl)methyl-indazoline-6-yl]-2,4-pyrimidinediamine. ¹H NMR (DMSO-d₆): δ 9.35 (s, 1H), 9.17 (s, 1H), 8.07 (d, 1H, J= 4.8 Hz), 7.92 (s, 1H),

7.89 (s, 1H), 7.66 (q, 1H, J= 4.7 Hz), 7.54 (d, 1H, J= 8.8 Hz), 7.35-7.24 (m, 3H), 6.76 (d, 1H, J= 8.8 Hz), 4.77 (s, 2H), 4.20 (s, 4H), 2.57 (d, 3H, J= 4.7 Hz). LCMS: ret. time: 15.82 min.; purity: 94%; MS (*m/e*): 450 (MH⁺).

7.3.593 R935213: N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(2-(N-methylamino)carbonyl-fur-4-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine

In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(2-methoxycarbonyl-fur-4-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine was reacted with Me₂NH.HCl and *i*-Pr₂NEt. to give N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(2-(N-methylamino)carbonyl-fur-4-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine. ¹H NMR (DMSO-d₆): δ 9.17 (s, 2H), 8.30 (q, 1H, J= 4.7 Hz), 8.05 (d, 1H, J= 3.5 Hz), 7.42 (s, 1H), 7.29-7.19 (m, 2H), 7.09 (t, 1H, J= 8.2 Hz), 7.02 (d, 1H, J= 2.9 Hz), 6.76 (d, 1H, J= 8.8 Hz), 6.67 (d, 1H, J= 2.9 Hz), 6.54 (dd, 1H, J= 1.7 and 8.2 Hz), 4.94 (s, 2H), 4.21-4.18 (m, 4H), 2.70 (d, 3H, J= 4.7 Hz). LCMS: ret. time: 18.85 min.; purity: 91%; MS (*m/e*): 492 (MH⁺).

7.3.594 R935216: 5-Fluoro-N2-[4-(N-methylamino)carbonylmethyleneoxyphenyl]-N4-(1-methyl-indazoline-5-yl)-2,4-pyrimidinediamine

In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, 5-fluoro-N2-[4-(methoxycarbonylmethyleneoxy)phenyl]-N4-(1-methyl-indazoline-5-yl)-2,4-pyrimidinediamine and Me₂NH.HCl were reacted to provide 5-fluoro-N2-[4-(N-methylamino)carbonylmethyleneoxyphenyl]-N4-(1-methyl-indazoline-5-yl)-2,4-pyrimidinediamine ¹H NMR (DMSO-d₆): δ 9.31 (s, 1H), 9.00 (s, 1H), 8.17 (s, 1H), 8.02 (d, 1H, J= 3.5 Hz), 7.99 (m, 1H), 7.93 (s, 1H), 7.59 (m, 2H), 7.52 (d, 2H, J= 8.8 Hz), 6.78 (d, 2H, J= 8.8 Hz), 4.36 (s, 2H), 4.03 (s, 3H), 2.63 (d, 3H, J= 4.7 Hz). LCMS: ret. time: 14.81 min.; purity: 99%; MS (*m/e*): 422 (MH⁺).

7.3.595 R935217: N2, N4-Bis[1-(N-methylaminocarbonyl)methyl-indazoline-5-yl]-5-fluoro-2,4-pyrimidinediamine

In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, N2, N4-bis[1-(methoxycarbonyl)methyl-indazoline-6-yl]-5-fluoro-2,4-pyrimidinediamine and

Me₂NH.HCl were reacted to produce N2, N4-bis[1-(N-methylaminocarbonyl)methyl-indazoline-5-yl]-5-fluoro-2,4-pyrimidinediamine. ¹H NMR (DMSO-d₆): δ 9.35 (s, 1H), 9.15 (s, 1H), 8.09-8.06 (m, 2H), 7.97-7.96 (m, 2H), 7.91 (s, 1H), 7.70 (s, 1H), 7.69 (s, 1H), 7.64-7.55 (m, 2H), 7.48-7.40 (m, 2H), 5.06 (s, 2H), 4.97 (s, 2H), 2.62 (d, 3H, J= 4.7 Hz), 2.61 (d, 3H, J= 4.7 Hz). LCMS: ret. time: 12.54 min.; purity: 95%; MS (*m/e*): 503 (MH⁺).

7.3.596 N4-(3,4-Ethylenedioxyphenyl)-5-fluoro-N2-[3-[2-(N-morpholino)ethyleneoxy]phenyl]-2,4-pyrimidinediamine (R926486)

A dry reaction vial equipped with a rubber septum was charged with N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-morpholino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (0.019 g, 0.04 mmol) and THF (1 mL). To this was added boranemethyl sulfide complex (0.044 mL, 0.088 mmol) and stirred at room temperature for 2h. The amount of boranemethyl sulfide complex was evaporated and the reaction was quenched with MeOH (CAUTION: vigorous evolution of hydrogen gas occurs during the addition of MeOH), heated for 30 min. The solvent was removed and again the residue was suspended in MeOH, extracted with EtOAc, EtOAc was evaporated and the residue was purified by preparative TLC to obtain N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-[2-(N-morpholino)ethyleneoxy]phenyl]-2,4-pyrimidinediamine. ¹H NMR (CDCl₃): δ 8.20 (s, 1H), 8.01 (d, 1H, J= 6 Hz), 7.26-7.05 (m, 3H), 7.05-6.97 (m, 3H), 6.82 (d, 1H, J= 9.3 Hz), 6.67 (dd, 1H, J= 1.8 and 8.1 Hz), 4.44 (t, 2H), 4.27 (s, 4H), 4.14 (m, 2H), 3.76 (m, 2H), 3.22 (t, 2H, J= 5.4 Hz), 3.05 (m, 2H), 2.88 (m, 2H).

7.3.597 N4-(3,4-Ethylenedioxyphenyl)-5-fluoro-N2-[2-(N-morpholinomethylene)benzofuran-5-yl]-2,4-pyrimidinediamine (R926490)

In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-[2-(N-morpholino)ethyleneoxy]phenyl]-2,4-pyrimidinediamine, the reaction of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[2-(N-morpholino)carbonylbzenzofuran-5-yl]-2,4-pyrimidinediamine with boranemethyl sulfide complex gave N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[2-(N-morpholinomethylene)benzofuran-5-yl]-2,4-pyrimidinediamine. ¹H NMR (CD₃OD): δ 8.65 (d, 2H, J= 2.1 Hz), 8.30 (dd, 2H, J= 2.1 and 9.6 Hz), 7.73 (d, 2H, J= 9.3 Hz), 7.49 (bs, 2H), 7.32 (m, 1H), 6.74 (m, 1H), 4.24 (s, 4H), 3.97 (s, 2H), 3.78 (m, 4H), 3.56 (m, 4H).

7.3.598 N4-(3,4-Ethylenedioxyphenyl)-5-fluoro-N2-[3-[2-(N-methylamino)ethyleneoxy]phenyl]-2,4-pyrimidinediamine (R926510)

In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-[2-(N-morpholino)ethyleneoxy]phenyl]-2,4-pyrimidinediamine, N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine and boranemethyl sulfide complex gave N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-[2-(N-methylamino)ethyleneoxy]phenyl]-2,4-pyrimidinediamine. ¹H NMR (CD₃OD): δ 8.00 (d, 1H, J= 5.2 Hz), 7.50-7.30 (m, 2H), 7.16- 6.80 (m, 5H), 4.28 (m, 1H), 4.27 (bs, 4H), 4.22 (m, 1H), 3.44 (m, 2H), 2.79 (d, 3H, J= 3Hz); LCMS: ret. time: 15.64 min.; purity: 96%; MS (m/e): 412 (MH⁺).

7.3.599 5-Fluoro-N4-(3-hydroxyphenyl)-N2-[2-(N-piperazinomethylene)benzofuran-5-yl]-2,4-pyrimidinediamine (R926770)

In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-[2-(N-morpholino)ethyleneoxy]phenyl]-2,4-pyrimidinediamine, the reaction of 5-fluoro-N4-(3-hydroxyphenyl)-N2-[2-(N-piperazino)carbonylbenzofuran-5-yl]-2,4-pyrimidinediamine with boranemethyl sulfide complex gave 5-fluoro-N4-(3-hydroxyphenyl)-N2-[2-(N-piperazinomethylene)benzofuran-5-yl]-2,4-pyrimidinediamine. LCMS: ret. time: 12.06 min.; purity: 75%; MS (m/e): 435 (MH⁺).

7.3.600 N4-(3,5-Dimethyl-4-hydroxyphenyl)-5-fluoro-N2-[3-[2-(N-morpholino)ethyleneoxy]phenyl]-2,4-pyrimidinediamine (R940255)

In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-[2-(N-morpholino)ethyleneoxy]phenyl]-2,4-pyrimidinediamine, the reaction of N4-(3,5-dimethyl-4-hydroxyphenyl)-5-fluoro-N2-[3-(N-morpholino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine with boranemethyl sulfide complex gave N4-(3,5-dimethyl-4-hydroxyphenyl)-5-fluoro-N2-[3-[2-(N-morpholino)ethyleneoxy]phenyl]-2,4-pyrimidinediamine. LCMS: ret. time: 15.94 min.; purity: 99 %; MS (m/e): 454 (MH⁺); ¹H NMR (DMSO-d₆): δ 9.16 (1H, s), 9.07 (1H, s), 8.15 (1H, s), 8.11 (1H, d, J= 3.9 Hz), 7.40-7.30 (4H, m), 7.13 (1H, t, 8.1 Hz), 6.55 (1H, dd, J= 8.1 Hz, 3.2 Hz), 4.01 (2H, t, J= 5.7 Hz), 3.65 (4H, t, J= 4.2 Hz), 2.72 (2H, t, J= 5.7 Hz), 2.515 (4H, t, J= 4.5 Hz), 2.24 (6H, s).

7.3.601 N4-(3,5-Dimethyl-4-hydroxyphenyl)-5-fluoro-N2-[3-[2-(N-piperazino)ethoxy]phenyl]-2,4-pyrimidinediamine bis Hydrogen Chloride Salt (R945142)

In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-[2-(N-morpholino)ethyleneoxy]phenyl]-2,4-pyrimidinediamine, N4-(3,5-dimethyl-4-hydroxyphenyl)-5-fluoro-N2-[3-(N-piperazino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine was treated with boranemethyl sulfide complex to give N4-(3,5-dimethyl-4-hydroxyphenyl)-5-fluoro-N2-[3-[2-(N-piperazino)ethoxy]phenyl]-2,4-pyrimidinediamine, which was then treated with 4N HCl in dioxane (3 mL) followed by crystallization from MeOH/EtOAc to give N4-(3,5-dimethyl-4-hydroxyphenyl)-5-fluoro-N2-[3-[2-(N-piperazino)ethoxy]phenyl]-2,4-pyrimidinediamine bis Hydrogen Chloride Salt. ¹H NMR (CD₃OD): δ 2.17 (s, 6H), 3.66 (m, 10H), 4.26 (t, J= 4.5 Hz, 2H), 6.93 (dd, J= 1.5, 7.2 Hz, 1H), 7.10-7.13 (m, 2H), 7.17 (s, 2H), 7.31 (t, J= 8.4 Hz, 1H), 7.98 (d, J= 6.0 Hz, 1H); ¹⁹F NMR (282 MHz, CD₃OD): δ - 162.93; LCMS: ret. time: 13.25 min.; purity: 96.08%; MS (m/e): 453.09 (MH⁺).

7.3.602 N4-(3,4-Ethylenedioxyphenyl)-5-fluoro-N2-[4-(2-hydroxyethoxy)phenyl]-2,4-pyrimidinediamine (R945144)

In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-[2-(N-morpholino)ethyleneoxy]phenyl]-2,4-pyrimidinediamine, the reaction of N2-(4-carboxymethyleneoxyphenyl)-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine and boranemethyl sulfide complex gave N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[4-(2-hydroxyethoxy)phenyl]-2,4-pyrimidinediamine. ¹H NMR (acetone-*d*₆): δ 3.86 (t, J= 4.8 Hz, 2H), 4.04 (t, J= 4.8 Hz, 2H), 4.28 (m, 4H), 6.78 (d, J= 9.0 Hz, 1H), 6.86 (d, J= 9.0 Hz, 2H), 7.18 (dd, J= 2.7, 8.7 Hz, 1H), 7.47 (d, J= 2.7 Hz, 1H), 7.63 (d, J= 9.0 Hz, 2H), 7.91 (d, J= 3.6 Hz, 1H), 8.29 (br, 1H, NH), 8.31 (br, 1H, NH); ¹⁹F NMR (282 MHz, acetone-*d*₆): δ - 169.18; LCMS: ret. time: 17.41 min.; purity: 98.36%; MS (m/e): 399.01 (MH⁺).

7.3.603 N4-(3-Chloro-4-hydroxy-5-methylphenyl)-5-fluoro-N2-[3-[2-(N-piperazino)ethoxy]phenyl]-2,4-pyrimidinediamine Dihydrochloride Salt (R945150)

In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-[2-(N-morpholino)ethyleneoxy]phenyl]-2,4-pyrimidinediamine, N4-(3-chloro-4-hydroxy-5-methylphenyl)-5-fluoro-N2-[3-(N-piperazino)carbonylmethyleneoxyphenyl]-2,4-

pyrimidinediamine was treated with boranemethyl sulfide complex to give N4-(3-chloro-4-hydroxy-5-methylphenyl)-5-fluoro-N2-[3-[2-(N-piperazino)ethyloxy]phenyl]-2,4-pyrimidinediamine, which was then treated with 4N HCl in dioxane (3 mL) followed crystallization from MeOH/EtOAc to give N4-(3-chloro-4-hydroxy-5-methylphenyl)-5-fluoro-N2-[3-[2-(N-piperazino)ethoxy]phenyl]-2,4-pyrimidinediamine bis Hydrogen Chloride Salt. ¹H NMR (CD₃OD): δ 2.21 (s, 3H), 3.72 (m, 10H), 4.35 (t, J= 4.5 Hz, 2H), 6.95 (dt, J= 1.5 and 9.0 Hz, 1H), 7.11-7.14 (m, 2H), 7.26 (dd, J= 0.9 and 2.7 Hz, 1H), 7.34 (t, J= 8.4 Hz, 1H), 7.50 (d, J= 2.4 Hz, 1H), 8.03 (d, J= 5.4 Hz, 1H); ¹⁹F NMR (282 MHz, CD₃OD): δ - 162.74; LCMS: ret. time: 14.50 min.; purity: 94.75%; MS (m/e): 472.98 (MH⁺).

7.3.604 N4-(3,5-Dimethyl-4-methoxyphenyl)-5-fluoro-N2-[3-[2-(N-piperazino)ethoxy]phenyl]-2,4-pyrimidinediamine Dihydrochloride Salt (R945157)

In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-[2-(N-morpholino)ethyleneoxy]phenyl]-2,4-pyrimidinediamine, N4-(3,5-dimethyl-4-methoxyphenyl)-5-fluoro-N2-[3-(N-piperazino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine was treated with boranemethyl sulfide complex to give N4-(3,5-dimethyl-4-methoxyphenyl)-5-fluoro-N2-[3-[2-(N-piperazino)ethyloxy]phenyl]-2,4-pyrimidinediamine, which was then treated with 4N HCl in dioxane (3 mL) followed crystallization from MeOH/EtOAc to give N4-(3,5-dimethyl-4-methoxyphenyl)-5-fluoro-N2-[3-[2-(N-piperazino)ethoxy]phenyl]-2,4-pyrimidinediamine bis Hydrogen Chloride Salt. ¹H NMR (CD₃OD): δ 2.23 (s, 6H), 3.66 (m, 10H), 3.72 (s, 3H), 4.31 (t, J= 4.5 Hz, 2H), 6.95 (dd, J= 1.8 and 8.4 Hz, 1H), 7.09-7.15 (m, 2H), 7.27 (s, 2H), 7.32 (t, J= 8.1 Hz, 1H), 8.01 (d, J= 5.4 Hz, 1H); ¹⁹F NMR (282 MHz, CD₃OD): δ - 162.71; LCMS: ret. time: 16.41 min.; purity: 97.50%; MS (m/e): 467.12 (MH⁺).

7.3.605 N4-(3,4-Ethylenedioxyphenyl)-5-fluoro-N2-[2-(N-piperazino)carbonylbenzofuran-5-yl]-2,4-pyrimidinediamine Hydrogen Chloride Salt (R926501)

The reaction of equivalent amount of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[2-(N-piperazino)carbonylbenzofuran-5-yl]-2,4-pyrimidinediamine with hydrogen chloride (4M, dioxane) in methanol at 0 °C followed by dilution with dry ethyl ether or ethyl acetate gave the precipitate. The resulting precipitate was isolated by filtration (and/or using centrifuse technique) to give N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[2-(N-

piperazino)carbonylbenzofuran-5-yl]-2,4-pyrimidinediamine Hydrogen Chloride Salt. ¹H NMR (CD₃OD): δ 7.97 (d, 1H, J= 5.4 Hz), 7.92 (d, 1H, J= 1.8 Hz), 7.62 (d, 1H, J= 8.2 Hz), 7.48 (s, 1H), 7.43 (dd, 1H, J= 2.4 and 8.7 Hz), 7.17 (d, 1H, J=2.4 Hz), 6.98 (dd, 1H, J= 2.4 and 8.7 Hz), 6.77 (d, 1H, J= 8.7 Hz), 4.13 (m, 4H), 4.22 (s, 4H), 3.38 (t, 4H, J= 5.7 Hz); LCMS: ret. time: 15.12 min; purity: 89%; MS (m/e): 491 (MH⁺).

7.3.606 N4-(3,4-Ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-piperazino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine Hydrogen Chloride Salt (R926504)

In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[2-(N-piperazino)carbonylbenzofuran-5-yl]-2,4-pyrimidinediamine Hydrogen Chloride Salt, the reaction of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-piperazino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine and hydrogen chloride gave N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-piperazino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine Hydrogen Chloride Salt. ¹H NMR (DMSO-d₆): δ 9.6 (bs, 1H), 9.04 (bs, 1H), 8.12 (d, 1H, J= 3.6 Hz), 7.25-7.00 (m, 5H), 7.81 (d, 1H, J= 8.7 Hz), 6.54 (d, 1H, J= 8.4 Hz), 4.74 (s, 2H), 4.22 (s, 4H), 3.64 (m, 4H), 3.11 (m, 4H); LCMS: ret. time: 15.34 min.; purity: 100%; MS (m/e): 481 (MH⁺).

7.3.607 N4-(3,4-Ethylenedioxyphenyl)-5-fluoro-N2-[3-(2-N-methylaminoethyl)phenyl]-2,4-pyrimidinediamine Hydrogen Chloride Salt (R926509)

In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[2-(N-piperazino)carbonylbenzofuran-5-yl]-2,4-pyrimidinediamine Hydrogen Chloride Salt, the reaction of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-[2-(N-methylamino)ethyloxy]phenyl]-2,4-pyrimidinediamine with hydrogen chloride (4M, dioxane) gave N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-[2-(N-methylamino)ethyloxy]phenyl]-2,4-pyrimidinediamine Hydrogen Chloride Salt. LCMS: ret. time: 15.88 min.; purity: 92%; MS (m/e): 412 (MH⁺).

7.3.608 N4-(3,4-Ethylenedioxyphenyl)-5-fluoro-N2-[3-[2-(N-morpholino)ethyloxy]phenyl]-2,4-pyrimidinediamine Hydrogen Chloride Salt (R926511)

In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[2-(N-piperazino)carbonylbenzofuran-5-yl]-2,4-pyrimidinediamine Hydrogen Chloride Salt, the reaction of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-[2-(N-

morpholino)ethyloxy]phenyl]-2,4-pyrimidinediamine and hydrogen chloride gave N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-[2-(N-morpholino)ethyloxy]phenyl]-2,4-pyrimidinediamine Hydrogen Chloride Salt. ¹H NMR (CD₃OD): δ 7.98 (d, 1H, J= 5.4 Hz), 7.34 (t, 1H, 8.4 Hz), 7.16-6.81 (m, 6H), 4.42 (m, 1H), 4.40 (m, 2H), 4.25 (m, 5H), 4.10 (m, 2H), 3.90 (bs, 2H), 3.60 (m, 4H); LCMS: ret. time: 16.39 min.; purity: 100%; MS (m/e): 468 (MH⁺).

7.3.609 N4-(3,4-Ethylenedioxyphenyl)-5-fluoro-N2-[2-(N-homopiperazino)carbonylbenzofuran-5-yl]-2,4-pyrimidinediamine Hydrogen Chloride Salt (R926768)

In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[2-(N-piperazino)carbonylbenzofuran-5-yl]-2,4-pyrimidinediamine Hydrogen Chloride Salt, the reaction of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[2-(N-homopiperazino)carbonylbenzofuran-5-yl]-2,4-pyrimidinediamine with hydrogen chloride treatment gave N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[2-(N-homopiperazino)carbonylbenzofuran-5-yl]-2,4-pyrimidinediamine Hydrogen Chloride Salt. ¹H NMR (DMSO-d₆): δ 9.98 (bs, 1H), 9.05 (bs, 1H), 8.18 (d, 1H, J= 4.8 Hz), 8.01 (s, 1H), 7.58 (d, 1H, J= 8.7 Hz), 7.50 (bd, 1H), 7.35 (s, 1H), 7.24 (d, 1H, J= 2.4 Hz), 7.11 (dd, 1H, J= 3 and 9 Hz), 6.80 (d, 1H, J= 8.7 Hz), 4.22 (s, 4H), 4.20-3.60 (m, 8H), 3.20 (m, 2H); LCMS: ret. time: 14.91 min.; purity: 86%; MS (m/e): 505 (MH⁺).

7.3.610 5-Fluoro-N4-(3-hydroxyphenyl)-N2-[2-(N-piperazino)carbonylbenzofuran-5-yl]-2,4-pyrimidinediamine Hydrogen Chloride Salt R926502)

In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[2-(N-piperazino)carbonylbenzofuran-5-yl]-2,4-pyrimidinediamine Hydrogen Chloride Salt, 5-fluoro-N4-(3-hydroxyphenyl)-N2-[2-(N-piperazino)carbonylbenzofuran-5-yl]-2,4-pyrimidinediamine upon treatment with hydrogen chloride (4M, dioxane) gave 5-fluoro-N4-(3-hydroxyphenyl)-N2-[2-(N-piperazino)carbonylbenzofuran-5-yl]-2,4-pyrimidinediamine Hydrogen Chloride Salt. ¹H NMR (CDCl₃OD): δ 8.00 (s, 1H), 7.89 (s, 1H), 7.98 (s, 1H), 7.60 (d, 1H, J= 8.7 Hz), 7.45 (m, 3H), 7.16 (t, 1H, J= 8.1 Hz), 7.10 (m, 1H), 7.02 (dd, 1H, J= 1.2 and 7.2 Hz), 6.70 (dd, 1H, J= 2.4 and 8.4 Hz), 4.13 (m, 4H), 3.37 (t, 4H, J= 5.4 Hz), 3.38 (t, 4H, J= 5.7 Hz); LCMS: ret. time: 13.40 min; purity: 79%; MS (m/e): 450 (MH⁺).

7.3.611 5-Fluoro-N4-(3-hydroxyphenyl)-N2-[2-(N-piperazinomethylene)benzofuran-5-yl]-2,4-pyrimidinediamine Dihydrochloride Salt (R926769)

In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[2-(N-piperazino)carbonylbenzofuran-5-yl]-2,4-pyrimidinediamine Hydrogen Chloride Salt, the reaction of 5-fluoro-N4-(3-hydroxyphenyl)-N2-[2-(N-piperazinomethylene)benzofuran-5-yl]-2,4-pyrimidinediamine with hydrogen chloride (4M, dioxane) gave 5-fluoro-N4-(3-hydroxyphenyl)-N2-[2-(N-piperazinomethylene)benzofuran-5-yl]-2,4-pyrimidinediamine Dihydrochloride Salt. ¹H NMR (CD₃OD): δ 8.00 (d, 1H), 7.85 (bd, 1H), 7.75 (m, 3H), 7.60 (m, 2H), 7.40-7.15 (m, 4H), 7.05 (s, 1H), 7.00-6.800 (m, 3H), 4.65 (dd, 2H), 3.60 (m, 8H).

7.3.612 5-Fluoro-N4-(3-hydroxyphenyl)-N2-[3-(N-piperazino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine Hydrogen Chloride Salt (R926773)

In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[2-(N-piperazino)carbonylbenzofuran-5-yl]-2,4-pyrimidinediamine Hydrogen Chloride Salt, 5-fluoro-N4-(3-hydroxyphenyl)-N2-[3-(N-piperazino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine and hydrogen chloride (4M, dioxane) gave 5-fluoro-N4-(3-hydroxyphenyl)-N2-[3-(N-piperazino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine Hydrogen Chloride Salt. ¹H NMR (CD₃OD): δ 7.99 (d, 1H, J= 5.1 Hz), 7.29 (t, 1H, J= 8.1 Hz), 7.21-7.05 (m, 5H), 6.83 (dd, 1H, J= 2.4 and 8.7 Hz), 6.77 (bd, 1H), 4.79 (s, 2H), 3.83 (m, 2H), 3.78 (m, 2H), 3.25 (m, 2H); LCMS: ret. time: 12.27 min.; purity: 91%; MS (m/e): 439 (MH⁺).

7.3.613 N2-[3-[2-(N, N-Dimethylamino)ethyloxy]phenyl]-N4-(3,4-Ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine Hydrogen Chloride Salt (R926771)

In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[2-(N-piperazino)carbonylbenzofuran-5-yl]-2,4-pyrimidinediamine Hydrogen Chloride Salt, the treatment of N4-(3,4-ethylenedioxyphenyl)-N2-[3-[2-(N, N-dimethylamino)ethyloxy]phenyl]-5-fluoro-2,4-pyrimidinediamine with equivalent amount of hydrogen chloride (4M, dioxane) gave N4-(3,4-ethylenedioxyphenyl)-N2-[3-[2-(N, N-dimethylamino)ethyloxy]phenyl]-5-fluoro-2,4-pyrimidinediamine Hydrogen Chloride Salt. LCMS: ret. time: 15.37 min.; purity: 93%; MS (m/e): 426 (MH⁺).

7.3.614 N4-(3,5-Dimethyl-4-hydroxyphenyl)-5-fluoro-N2-[3-[2-(N-morpholino)ethyloxy]phenyl]-2,4-pyrimidinediamine Hydrogen Chloride Salt (R940256)

In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[2-(N-piperazino)carbonylbenzofuran-5-yl]-2,4-pyrimidinediamine Hydrogen Chloride Salt, the reaction of N4-(3,5-dimethyl-4-hydroxyphenyl)-5-fluoro-N2-[3-[2-(N-morpholino)ethyloxy]phenyl]-2,4-pyrimidinediamine with hydrogen chloride (4M, dioxane) gave N4-(3,5-dimethyl-4-hydroxyphenyl)-5-fluoro-N2-[3-[2-(N-morpholino)ethyloxy]phenyl]-2,4-pyrimidinediamine Hydrogen Chloride Salt. LCMS: ret. time: 15.78 min.; purity: 98 %; MS (M/e): 454 (MH⁺); ¹H NMR (DMSO-d₆): δ 10.60 (1H, s), 9.58 (1H, s), 8.29 (1H, s), 8.20 (1H, s), 7.43 (1H, d, J= 9Hz), 7.38-7.30 (3H, m), 7.24 (1H, t, J= 9 Hz), 6.70 (1H, d, J= 9 Hz), 4.35 (2H, m), 4.05 (2H, m), 3.84 (4H, m), 3.65-3.50 (2H, m), 3.26 (2H, m), 2.25 (6H, s).

7.3.615 N4-(3-Chloro-4-hydroxy-5-methylphenyl)-5-fluoro-N2-[3-[2-(N-morpholino)ethyloxy]phenyl]-2,4-pyrimidinediamine Hydrogen Chloride Salt (R940269)

In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[2-(N-piperazino)carbonylbenzofuran-5-yl]-2,4-pyrimidinediamine Hydrogen Chloride Salt, the reaction of N4-(3-chloro-4-hydroxy-5-methylphenyl)-5-fluoro-N2-[3-[2-(N-morpholino)ethyloxy]phenyl]-2,4-pyrimidinediamine with hydrogen chloride (4M, dioxane) gave N4-(3-chloro-4-hydroxy-5-methylphenyl)-5-fluoro-N2-[3-[2-(N-morpholino)ethyloxy]phenyl]-2,4-pyrimidinediamine Hydrogen Chloride Salt. LCMS: ret. time: 14.74 min.; purity: 96 %; MS (m/e): 474 (M⁺), 475 (MH⁺); ¹H NMR (DMSO-d₆): δ 10.03 (1H, s), 9.35 (2H, s), 9.06 (1H, s), 8.17 (1H, d, J= 3.9 Hz), 7.67 (1H, m), 7.52 (1H, m), 7.46 (1H, d, J= 8.7 Hz), 7.39 (1H, s), 7.24 (1H, t, J= 8.1 Hz), 6.66 (1H, d, J= 8.1 Hz), 4.33 (1H, m), 4.07 (1H, d, J= 13 Hz), 3.79 (1H, t, J= 12.5 Hz), 3.56 (4H, m), 3.49 (4H, m), 3.29 (1H, t, J= 12.5 Hz), 2.29 (3H, s).

7.3.616 N4-(3,4-Ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine Hydrogen Chloride Salt (R926816)

In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[2-(N-piperazino)carbonylbenzofuran-5-yl]-2,4-pyrimidinediamine Hydrogen Chloride Salt, the treatment of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine with equivalent

amount of hydrogen chloride (4M, dioxane) gave the N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine Hydrogen Chloride salt. LCMS: ret. time: 17.04 min., purity: 96%, MS (m/e): 426 (MH⁺).

7.3.617 N4-(3,4-Ethylenedioxy)-5-fluoro-N2-[2-(hydroxymethyl)benzofuran-5-yl]-2,4-pyrimidinediamine (R926696)

A dry reaction flask charged with N4-(3,4-Ethylenedioxyphenyl)-5-fluoro-N2-(2-methoxycarbonylbenzofuran-5-yl)-2,4-pyrimidinediamine was reacted with diisobutylaluminum hydride (DIBALH) (5 equivalents) in CH₂Cl₂ at -78 °C (reaction was monitored by TLC) followed by treatment with Rochell's salt to yield N4-(3,4-ethylenedioxy)-5-fluoro-N2-[2-(hydroxymethyl)benzofuran-5-yl]-2,4-pyrimidinediamine. ¹H NMR (DMSO-d₆): δ 9.11 (s, 1H), 8.02 (d, 1H, J = 3.3 Hz), 7.96 (t, 1H, J = 1.8 Hz), 7.40-7.30 (m, 3H), 7.19 (dt, 1H, J = 3.6 and 8.1 Hz), 6.78 (d, 1H, J = 8.7 Hz), 6.59 (s, 1H), 4.52 (d, 2H, J = 5.1 Hz), 4.22 (s, 4H); ¹⁹F NMR (DMSO-d₆): - 46802; LCMS: ret. time: 19.14 min.; purity: 95 %; MS (m/e): 409 (MH⁺).

7.3.618 5-Fluoro-N4-(3-hydroxyphenyl)-N2-[2-(hydroxymethyl)-(1H)-indol-5-yl]-2,4-pyrimidinediamine (R926700)

In a manner similar to the preparation of N4-(3,4-ethylenedioxy)-5-fluoro-N2-[2-(hydroxymethyl)benzofuran-5-yl]-2,4-pyrimidinediamine, 5-fluoro-N4-(3-hydroxyphenyl)-N2-[2-(methoxycarbonyl)-(1H)-indol-5-yl]-2,4-pyrimidinediamine was reduced with DIBALH to yield 5-fluoro-N4-(3-hydroxyphenyl)-N2-[2-(hydroxymethyl)-(1H)-indol-5-yl]-2,4-pyrimidinediamine. ¹H NMR (CD₃OD): δ 7.81 (d, 1H, J = 4.2 Hz), 7.23 (d, 1H, J = 1.8 Hz), 7.28-7.23 (m, 2H), 7.19 (t, 1H, J = 2.4 Hz), 7.12 (dd, 1H, J = 1.8 and 9.0 Hz), 7.07 (t, 1H, J = 8.4 Hz), 6.52 (ddd, 1H, J = 1.2 and 8.1 Hz), 6.30 (s, 1H), 4.71 (s, 2H); ¹⁹F NMR (CD₃OD): - 47971; LCMS: ret. time: 15.36 min.; purity: 100 %; MS (m/e): 366 (MH⁺).

7.3.619 5-Fluoro-N2-[2-(hydroxymethyl)benzofuran-5-yl]-N4-[4-(isopropoxy)phenyl]-2,4-pyrimidinediamine (R926705)

In a manner similar to the preparation of N4-(3,4-ethylenedioxy)-5-fluoro-N2-[2-(hydroxymethyl)benzofuran-5-yl]-2,4-pyrimidinediamine, 5-fluoro-N2-(2-methoxycarbonylbenzofuran-5-yl)-N4-(4-isopropoxyphenyl)-2,4-pyrimidinediamine was reduced with DIBALH to yield 5-fluoro-N2-[2-(hydroxymethyl)benzofuran-5-yl]-N4-(4-isopropoxyphenyl)-2,4-pyrimidinediamine. ¹H NMR (CD₃OD): δ 7.83 (d, 1H, J = 3.3 Hz),

7.81 (s, 1H), 7.50 (d, 2H, J= 9.0 Hz), 7.29 (d, 1H, J= 9.0 Hz), 7.22 (dd, 1H, J= 2.4 and 8.7 Hz), 6.84 (d, 2H, J= 8.7 Hz), 6.56 (d, 1H, J= 1.2 Hz), 4.64 (s, 2H), 4.56 (2q, 1H, J= 5.7 Hz), 1.31 (d, 6H, J= 6.0 Hz); ¹⁹F NMR (CD₃OD): - 47926; LCMS: ret. time: 21.03 min.; purity: 99 %; MS (m/e): 409 (MH⁺).

5 **7.3.620 5-Fluoro-N2-[2-(hydroxymethyl)benzofuran-5-yl]-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine (R926707)**

In a manner similar to the preparation of N4-(3,4-ethylenedioxy)-5-fluoro-N2-[2-(hydroxymethyl)benzofuran-5-yl]-2,4-pyrimidinediamine, 5-fluoro-N4-(3-hydroxyphenyl)-N2-[2-(methoxycarbonyl)benzofuran-5-yl]-2,4-pyrimidinediamine was reduced with
10 DIBALH to yield 5-fluoro-N2-[2-(hydroxymethyl)benzofuran-5-yl]-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine. ¹H NMR (DMSO-d₆): δ 9.37 (s, 1H), 9.17 (s, 1H), 9.12 (s, 1H), 8.06 (d, 1H, J= 3.9 Hz), 8.01 (d, 1H, J= 1.8 Hz), 7.41-7.35 (m, 2H), 7.26 (d, 1H, J= 8.1 Hz), 7.11-7.05 (m, 2H), 6.60 (s, 1H), 6.51 (dd, 1H, J= 2.4 and 8.4 Hz), 5.41 (t, 1H, J= 6.0 Hz), 4.51 (d, 2H, J= 5.7 Hz); LCMS: ret. time: 16.21 min.; purity: 95 %; MS (m/e): 367 (MH⁺).

15 **7.3.621 N4-(4-*tert*-Butyl)phenyl)-5-fluoro-N2-[3-(2-hydroxyethyleneoxy)phenyl]-2,4-pyrimidinediamine (R926728)**

In a manner similar to the preparation of N4-(3,4-ethylenedioxy)-5-fluoro-N2-[2-(hydroxymethyl)benzofuran-5-yl]-2,4-pyrimidinediamine, N4-(4-*tert*-butylphenyl)-5-fluoro-N2-(3-methoxycarbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine was reduced
20 with DIBAL to yield N4-(4-*tert*-butylphenyl)-5-fluoro-N2-[3-(2-hydroxyethyleneoxy)phenyl]-2,4-pyrimidinediamine. ¹H NMR (CDCl₃): δ 7.94 (d, 1H, J= 3.0 Hz), 7.54 (d, 2H, J= 9.0 Hz), 7.37 (d, 2H, J= 8.4 Hz), 7.29-7.35 (m, 1H), 7.19-7.14 (m, 2H), 7.06 (d, 1H, J= 8.1 Hz), 6.82 (d, 1H, J= 2.7 Hz), 6.57 (dd, 1H, J= 2.4 and 8.1 Hz), 4.04-4.00 (m, 2H), 3.93-
25 3.89 (m, 2H), 1.33 (s, 9H); ¹⁹F NMR (CDCl₃): -47214; LCMS: ret. time: 22.39 min.; purity: 94 %; MS (m/e): 397 (MH⁺).

7.3.622 5-(Hydroxymethyl)-N2-[3-(2-hydroxyethyleneoxy)phenyl]-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine (R926735)

In a manner similar to the preparation of N4-(3,4-ethylenedioxy)-5-fluoro-N2-[2-(hydroxymethyl)benzofuran-5-yl]-2,4-pyrimidinediamine, N4-(3-hydroxyphenyl)-5-methoxycarbonyl-N2-[3-(methoxycarbonylmethyleneoxy)phenyl]-2,4-pyrimidinediamine
30 was reduced with DIBALH to yield 5-(hydroxymethyl)-N2-[3-(2-

hydroxyethyleneoxy)phenyl]-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine. ¹H NMR (CD₃OD): δ 7.87 (s, 1H), 7.35 (t, 1H, J= 1.5 Hz), 7.15-7.08 (m, 5H), 6.57-6.50 (m, 2H), 4.56 (s, 2H), 3.92-3.86 (m, 2H), 3.84-3.79 (m, 2H); LCMS: ret. time: 14.11 min.; purity: 89 %; MS (m/e): 369 (MH⁺).

5 **7.3.623 5-Fluoro-N2-[3-(2-hydroxyethyleneoxy)phenyl]-N4-(3-isopropylphenyl)-2,4-pyrimidinediamine R940289**

In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-[2-(N-morpholino)ethyleneoxy]phenyl]-2,4-pyrimidinediamine, 5-fluoro-N4-(3-isopropylphenyl)-N2-(3-methoxycarbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine
10 reacted with DIBALH to give 5-fluoro-N2-[3-(2-hydroxyethyleneoxy)phenyl]-N4-(3-isopropylphenyl)-2,4-pyrimidinediamine. LCMS: ret. time: 23.03 min.; purity: 93 %; MS (m/e): 382 (M⁺), 384 (MH⁺); ¹H NMR (DMSO-d₆): δ 9.36 (1H, s), 9.24 (1H, s), 8.20 (1H, d, J= 4.2 Hz), 7.85 (1H, d, J= 8.5 Hz), 7.57 (1H, s), 7.41 (1H, s), 7.33 (1H, t, J= 8.5 Hz), 7.17 (1H, t, J= 8.5 Hz), 7.05 (1H, d, J= 8.5 Hz), 6.56 (1H, dd, J= 8.5 Hz, J= 2 Hz), 4.94 (1H, t, J= 12 Hz), 3.94 (2H, t, J= 4.7 Hz), 3.76 (2H, m), 2.95 (1H, sept, J= 6.9 Hz), 1.28 (6H, dd, J= 6.9 Hz, J= 0.6 Hz).
15

7.3.624 N4-(3-*tert*-Butylphenyl)-5-fluoro-N2-[2-(hydroxymethylene)benzofur-5-yl]-2,4-pyrimidinediamine R940287

20 In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-[2-(N-morpholino)ethyleneoxy]phenyl]-2,4-pyrimidinediamine, N4-(3-*tert*-butylphenyl)-5-fluoro-N2-(2-methoxycarbonylbenzofur-5-yl)-2,4-pyrimidinediamine reacted with DIBALH to give N4-(3-*tert*-butylphenyl)-5-fluoro-N2-[2-(hydroxymethylene)benzofur-5-yl]-2,4-pyrimidinediamine. LCMS: retn, time: 23.15 min.; purity: 99 %; MS (m/e): 407 (MH⁺); ¹H NMR (DMSO-d₆): δ 9.34 (1H, s), 9.22 (1H, s), 8.18 (1H, d, J= 3.9 Hz), 8.04 (1H, s), 8.00 (1H, d, J= 8.7 Hz), 7.60 (1H, t, J= 2.1 Hz), 7.47 (2H, m), 7.34 (1H, t, J= 7.8 Hz), 7.21 (1H, d, J= 8.7 Hz), 6.69 (1H, s), 5.54 (1H, t, J= 5.8 Hz), 4.63 (2H, d, J= 5.8 Hz), 1.35 (9H, s).
25

30 **7.3.625 5-Fluoro-N4-(3-isopropylphenyl)-N2-[2-(hydroxymethylene)benzofur-5-yl]-2,4-pyrimidinediamine R940286**

In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-[2-(N-morpholino)ethyleneoxy]phenyl]-2,4-pyrimidinediamine, 5-fluoro-N4-(3-

isopropylphenyl)-N2-(2-methoxycarbonylbenzofur-5-yl)-2,4-pyrimidinediamine reacted with DIBALH to give 5-fluoro-N4-(3-isopropylphenyl)-N2-[(2-hydroxymethylene)benzofur-5-yl]-2,4-pyrimidinediamine. LCMS: ret. time: 21.93 min.; purity: 99 %; MS (m/e): 393 (MH⁺); ¹H NMR (DMSO-d₆): δ 9.33 (1H, s), 9.23 (1H, s), 8.18 (1H, d, J= 3.9 Hz), 8.03 (1H, s), 7.86 (1H, d, J= 7.1 Hz), 7.57 (1H, s), 7.49 (2H, m), 7.33 (1H, t, J= 7.1 Hz), 7.05 (1H, d, J= 7.1 Hz), 6.69 (1H, s), 5.54 (1H, t, J= 5.7 Hz), 4.63 (2H, d, J= 5.7 Hz), 2.90 (1H, sept, J= 6.9 Hz), 1.26 (6H, d, J= 6.9 Hz).

7.3.626 N4-(3-*tert*-Butylphenyl)-5-fluoro-N2-[3-(2-hydroxyethyleneoxy)phenyl]-2,4-pyrimidinediamine R940282

In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-[2-(N-morpholino)ethyleneoxy]phenyl]-2,4-pyrimidinediamine, N4-(3-*tert*-butylphenyl)-5-fluoro-N2-(3-methoxycarbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine reacted with DIBALH to give N4-(3-*tert*-butylphenyl)-5-fluoro-N2-[3-(2-hydroxyethyleneoxy)phenyl]-2,4-pyrimidinediamine.

LCMS: ret. time: 21.63 min.; Purity: 98 %; MS (m/e): 396 (M⁺).

7.3.627 N4-[3,4-Bis(hydroxymethyl)phenyl]-5-fluoro-N2-[3-(2-hydroxyethyleneoxy)phenyl]-2,4-pyrimidinediamine (R940292)

In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-[2-(N-morpholino)ethyleneoxy]phenyl]-2,4-pyrimidinediamine, N2-(3-methoxycarbonylmethyleneoxyphenyl)-N4-[6-(3,3-dihydroisobenzofuranyl-1-one)]-5-fluoro-2,4-pyrimidinediamine reacted with DIBALH to give N4-[3,4-bis(hydroxymethyl)phenyl]-5-fluoro-N2-[3-(2-hydroxyethyleneoxy)phenyl]-2,4-pyrimidinediamine. LCMS: retn, time: 13.06 min.; purity: 100 %; MS (m/e): 400 (M⁺).

7.3.628 (R935149): N2-(3,4-Ethylenedioxyphenyl)-N4-[4-(2-hydroxy-1,1-dimethylethyl)phenyl]-5-fluoro-2,4-pyrimidinediamine

2-Chloro-5-fluoro-N4-[4-[ethoxycarbonyl(dimethyl)methyl]phenyl]-N2-(3,4-ethylenedioxyphenyl)-2,4-pyrimidinediamine was reduced with 10 eq. DIBALH (1.0 M in toluene) at 0 °C in dichloromethane. Reaction was quenched with methanol, diluted with ethylacetate followed by the addition of aqueous Rochelle's salt solution, stirred at room temperature for 30 minutes followed by the addition of anhydrous sodium sulfate. The solution was filtered through Celite, concentrated and purified the concentrated by silica gel

column chromatography to furnish the N2-(3,4-ethylenedioxyphenyl)-N4-[4-(2-hydroxy-1,1-dimethylethyl)phenyl]-5-fluoro-2,4-pyrimidinediamine. ¹H NMR (DMSO-d₆): δ 10.01 (br s, 1H), 9.6 (br s, 1H), 8.13 (d, 1H, J= 4.7 Hz), 7.58 (d, 2H, J= 8.2 Hz), 7.31 (d, 2H, J= 8.8 Hz), 7.18 (d, 1H, J= 2.3 Hz), 6.88 (dd, 1H, J= 2.3 and 8.8 Hz), 6.73 (d, 1H, J= 8.8 Hz), 4.21-4.19 (m, 4H), 3.56 (br s, 2H), 1.20 (s, 6H); LCMS: ret. time: 20.34 min.; purity: 98%; MS (*m/e*): 411 (MH⁺).

7.3.629 (R935151): 5-Fluoro-N2-[4-(2-hydroxy-1,1-dimethylethyl)phenyl]-N4-(4-isopropoxyphenyl)-2,4-pyrimidinediamine

In like manner to the preparation of N2-(3,4-ethylenedioxyphenyl)-5-fluoro-N4-[4-(2-hydroxy-1,1-dimethylethyl)phenyl]-2,4-pyrimidinediamine, N2-[4-[(1-ethoxycarbonyl-1-methyl)ethyl]phenyl]-5-fluoro-N4-(4-isopropoxyphenyl)-2,4-pyrimidinediamine was reduced with DIBALH to provide 5-fluoro-N2-[4-(2-hydroxy-1,1-dimethylethyl)phenyl]-N4-(4-isopropoxyphenyl)-2,4-pyrimidinediamine. ¹H NMR (CDCl₃): δ 7.89 (d, 1H, J= 2.9 Hz), 7.46 (d, 3H, J= 8.8 Hz), 7.27 (d, 2H, J= 8.2 Hz), 6.89 (d, 2H, J= 9.3 Hz), 6.68-6.65 (m, 1H), 4.53 (septet, 1H, J= 5.8 Hz), 3.57 (s, 2H), 1.36 (d, 6H, J= 5.8 Hz), 1.31 (s, 6H); LCMS: ret. time: 23.43 min.; purity: 99%; MS (*m/e*): 411 (MH⁺).

7.3.630 (R935153): 5-Fluoro-N2-[4-(2-hydroxy-1,1-dimethylethyl)phenyl]-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine:

In like manner to the preparation of N2-(3,4-ethylenedioxyphenyl)-5-fluoro-N4-[4-(2-hydroxy-1,1-dimethylethyl)phenyl]-2,4-pyrimidinediamine, N2-[4-[ethoxycarbonyl(dimethyl)methyl]phenyl]-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine was reduced with DIBALH to provide 5-fluoro-N2-[4-(2-hydroxy-1,1-dimethylethyl)phenyl]-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine. ¹H NMR (CDCl₃): δ 7.89 (d, 1H, J= 2.9 Hz), 7.57 (s, 1H), 7.41 (d, 2H, J= 8.8 Hz), 7.29 (d, 2H, J= 8.2 Hz), 7.16 (d, 1H, J= 8.2 Hz), 7.10 (d, 1H, J= 8.8 Hz), 6.80-6.55 (m, 2H), 5.58 (s, 2H), 1.30 (s, 6H); LCMS: ret. time: 18.01 min.; purity: 98%; MS (*m/e*): 369 (MH⁺).

7.3.631 (R935154): N4-(3,4-Ethylenedioxyphenyl)-5-fluoro-N2-[3-(2-hydroxyethoxy)phenyl]-2,4-pyrimidinediamine

In like manner to the preparation of N2-(3,4-ethylenedioxyphenyl)-5-fluoro-N4-[4-(2-hydroxy-1,1-dimethylethyl)phenyl]-2,4-pyrimidinediamine, N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-methoxycarbonylmethyleneoxyoxyphenyl)-2,4-

pyrimidinediamine was reduced with DIBALH to provide N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(2-hydroxyethoxy)phenyl]-2,4-pyrimidinediamine. ¹H NMR (CDCl₃): δ 7.88 (d, 1H, J= 3.8 Hz), 7.34 (t, 1H, J= 2.3 Hz), 7.19 (dd, 1H, J= 2.3 and 8.2 Hz), 7.14 (d, 1H, J= 7.6 Hz), 7.01-6.97 (m, 2H), 6.84 (d, 1H, J= 8.8 Hz), 6.53 (dd, 1H, J= 1.7 and 7.6 Hz), 4.26 (s, 4H), 3.98 (t, 2H, J= 4.1 Hz), 3.89 (t, 2H, J= 4.1 Hz); LCMS: ret. time: 18.36 min.; purity: 99%; MS (*m/e*): 399 (MH⁺).

7.3.632 (R935155): 5-Fluoro-N2-[4-(2-hydroxyethoxy)phenyl]-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine:

In like manner to the preparation of N2-(3,4-ethylenedioxyphenyl)-5-fluoro-N4-[4-(2-hydroxy-1,1-dimethylethyl)phenyl]-2,4-pyrimidinediamine, 5-fluoro-N4-(3-hydroxyphenyl)-N2-[4-(methoxycarbonylmethyleneoxy)phenyl]-2,4-pyrimidinediamine was reduced to 5-fluoro-N2-[4-(2-hydroxyethoxy)phenyl]-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine with DIBALH. ¹H NMR (CDCl₃): δ 7.73 (d, 1H, J= 3.5 Hz), 7.33 (d, 2H, J= 8.8 Hz), 7.15 (br s, 1H), 7.04 (app t, 2H, J= 8.2 and 7.6 Hz), 6.78 (d, 2H, J= 8.8 Hz), 6.49 (d, 1H, J= 7.6 Hz), 3.95 (t, 2H, J= 4.7 Hz), 3.80 (t, 2H, J= 4.7 Hz); LCMS: ret. time: 14.49 min.; purity: 98%; MS (*m/e*): 357 (MH⁺).

7.3.633 (R935156): 5-Fluoro-N2-[3-(2-hydroxyethoxy)phenyl]-N4-(4-isopropoxyphenyl)-2,4-pyrimidinediamine

In like manner to the preparation of N2-(3,4-ethylenedioxyphenyl)-5-fluoro-N4-[4-(2-hydroxy-1,1-dimethylethyl)phenyl]-2,4-pyrimidinediamine, 5-fluoro-N4-(4-isopropoxyphenyl)-N2-(3-methoxycarbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine was reduced with DIBALH to provide 5-fluoro-N2-[3-(2-hydroxyethoxy)phenyl]-N4-(4-isopropoxyphenyl)-2,4-pyrimidinediamine. ¹H NMR (CDCl₃): δ 7.90 (d, 1H, J= 3.5 Hz), 7.45 (d, 2H, J= 8.8 Hz), 7.34 (t, 1H, J= 2.3 Hz), 7.13 (t, 1H, J= 8.2 Hz), 6.93 (m, 3H), 7.76 (d, 1H, J= 2.3 Hz), 6.52 (dd, 1H, J= 2.3 and 8.2 Hz), 4.52 (septet, 1H, J= 5.7 Hz), 3.95-3.85 (m, 4H), 1.34 (d, 6H, J= 5.7 Hz); LCMS: ret. time: 21.17 min.; purity: 98%; MS (*m/e*): 399 (MH⁺).

7.3.634 (R935158): 5-Fluoro-N4-[4-(2-hydroxy-1,1-dimethylethyl)phenyl]-N2-[4-(2-hydroxyethoxy)phenyl]-2,4-pyrimidinediamine:

In like manner to the preparation of N2-(3,4-ethylenedioxyphenyl)-5-fluoro-N4-[4-(2-hydroxy-1,1-dimethylethyl)phenyl]-2,4-pyrimidinediamine, N4-[4-[1-ethoxycarbonyl]-

methyl)ethyl]phenyl]-5-fluoro-N2-(4-methoxycarbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine was reduced with DIBALH to give 5-fluoro-N4-[4-(2-hydroxy-1,1-dimethylethyl)phenyl]-N2-[4-(2-hydroxyethoxy)phenyl]-2,4-pyrimidinediamine. ¹H NMR (CDCl₃): δ 7.83 (d, 1H, J= 3.5 Hz), 7.49 (d, 2H, J= 8.8 Hz), 7.35 (d, 2H, J= 8.8 Hz), 7.31 (d, 2H, J= 8.8 Hz), 6.82 (d, 2H, J= 8.8 Hz), 4.03 (t, 2H, J= 4.7 Hz), 3.89 (t, 2H, J= 4.7 Hz), 3.56 (s, 2H), 1.30 (s, 6H); LCMS: ret. time: 16.86 min.; purity: 96%; MS (*m/e*): 413 (MH⁺).

7.3.635 (R935160): 5-Fluoro-N2-[4-(2-hydroxyethoxy)phenyl]-N4-(4-isopropoxyphenyl)-2,4-pyrimidinediamine:

In like manner to the preparation of N2-(3,4-ethylenedioxyphenyl)-5-fluoro-N4-[4-(2-hydroxy-1,1-dimethylethyl)phenyl]-2,4-pyrimidinediamine, 5-fluoro-N4-(4-isopropoxyphenyl)-N2-(4-methoxycarbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine was reduced with DIBALH to give 5-fluoro-N2-[4-(2-hydroxyethoxy)phenyl]-N4-(4-isopropoxyphenyl)-2,4-pyrimidinediamine. ¹H NMR (DMSO-d₆): δ 9.12 (s, 1H), 8.92 (s, 1H), 7.98 (d, 1H, J= 3.5 Hz), 7.59 (d, 2H, J= 8.8 Hz), 7.49 (d, 2H, J= 9.3 Hz), 6.86 (d, 2H, J= 8.8 Hz), 6.76 (d, 2H, J= 9.3 Hz), 4.82 (t, 1H, J= 4.9 Hz), 4.55 (septet, 1H, J= 6.4 Hz), 3.89 (t, 2H, J= 5.3 Hz), 3.67 (app q, 2H, J= 5.3 and 4.9 Hz), 1.24 (d, 6H, J= 6.4 Hz); LCMS: ret. time: 19.56 min.; purity: 100%; MS (*m/e*): 399 (MH⁺).

7.3.636 (R935161): 5-Fluoro-N4-[4-(2-hydroxy-1,1-dimethylethyl)phenyl]-N2-[3-(2-hydroxyethoxy)phenyl]-2,4-pyrimidinediamine

In like manner to the preparation of N2-(3,4-ethylenedioxyphenyl)-5-fluoro-N4-[4-(2-hydroxy-1,1-dimethylethyl)phenyl]-2,4-pyrimidinediamine, N4-[4-(1-ethoxycarbonyl-1-methyl)ethylphenyl]-5-fluoro-N2-(3-methoxycarbonylmethylphenyl)-2,4-pyrimidinediamine was reduced with DIBALH to give 5-fluoro-N4-[4-(2-hydroxy-1,1-dimethylethyl)phenyl]-N2-[3-(2-hydroxyethoxy)phenyl]-2,4-pyrimidinediamine. ¹H NMR (DMSO-d₆): δ 9.27 (s, 1H), 9.11 (s, 1H), 8.07 (d, 1H, J= 3.5 Hz), 7.67 (d, 2H, J= 8.8 Hz), 7.38-7.24 (m, 4H), 7.06 (t, 1H, J= 8.2 Hz), 6.46 (dd, 1H, J= 8.2 Hz), 4.83 (t, 1H, J= 5.3 Hz), 4.66 (t, 1H, J= 5.3 Hz), 3.88 (t, 2H, J= 5.3 Hz), 3.67 (t, 1H, J= 5.3 Hz), 3.66 (t, 1H, J= 5.3 Hz), 3.38 (d, 2H, J= 5.3 Hz), 1.20 (s, 6H); LCMS: ret. time: 17.17 min.; purity: 96%; MS (*m/e*): 413 (MH⁺).

7.3.637 (R935168): 5-Fluoro-N4-[4-(2-hydroxy-1,1-dimethylethyl)phenyl]-N2-(4-isopropoxyphenyl)-2,4-pyrimidinediamine

In like manner to the preparation of N2-(3,4-ethylenedioxyphenyl)-5-fluoro-N4-[4-(2-hydroxy-1,1-dimethylethyl)phenyl]-2,4-pyrimidinediamine, N4-[4-(1-ethoxycarbonyl-1-methyl)ethylphenyl]-5-fluoro-N2-(4-isopropoxyphenyl)-2,4-pyrimidinediamine was reduced with DIBALH to produce 5-fluoro-N4-[4-(2-hydroxy-1,1-dimethylethyl)phenyl]-N2-(4-isopropoxyphenyl)-2,4-pyrimidinediamine. ¹H NMR (DMSO-d₆): δ 9.21 (s, 1H), 8.93 (s, 1H), 8.00 (d, 1H, J = 4.1 Hz), 7.62 (d, 2H, J = 8.8 Hz), 7.48 (d, 2H, J = 8.8 Hz), 7.27 (d, 2H, J = 8.8 Hz), 6.75 (d, 2H, J = 8.8 Hz), 4.65 (t, 1H, J = 5.3 Hz), 4.47 (septet, 1H, J = 5.8 Hz), 3.38 (d, 2H, J = 5.3 Hz), 1.22 (d, 6H, J = 5.8 Hz), 1.20 (s, 6H); LCMS: ret. time: 22.97 min.; purity: 99%; MS (*m/e*): 411 (MH⁺).

7.3.638 (R935170): 5-Fluoro-N4-[3-(2-hydroxyethoxy)phenyl]-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine:

In like manner to the preparation of N2-(3,4-ethylenedioxyphenyl)-5-fluoro-N4-[4-(2-hydroxy-1,1-dimethylethyl)phenyl]-2,4-pyrimidinediamine, 5-fluoro-N2-(3-hydroxyphenyl)-N4-(3-methoxycarbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine was reduced with DIBALH to produce 5-fluoro-N4-[3-(2-hydroxyethoxy)phenyl]-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine. ¹H NMR (DMSO-d₆): δ 9.23 (s, 1H), 9.14 (s, 1H), 9.06 (s, 1H), 8.07 (d, 1H, J = 4.1 Hz), 7.51 (dd, 1H, J = 1.7 and 7.6 Hz), 7.30 (app t, 1H, J = 2.3 and 1.7 Hz), 7.19 (t, 1H, J = 8.2 Hz), 7.13 (br s, 1H), 7.11 (m, 1H), 6.96 (t, 1H, J = 7.6 Hz), 6.61 (dd, 1H, J = 2.3 and 8.2 Hz), 6.28 (dd, 1H, J = 2.3 Hz and 8.2 Hz), 4.84 (t, 1H, J = 5.8 Hz), 3.92 (t, 2H, J = 5.2 Hz), 3.68 (app qt, 2H, J = 5.2 Hz); LCMS: ret. time: 14.71 min.; purity: 96%; MS (*m/e*): 357 (MH⁺).

7.3.639 (R935171): 5-Fluoro-N2-[4-(2-hydroxy-1,1-dimethylethyl)phenyl]-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine

In like manner to the preparation of N2-(3,4-ethylenedioxyphenyl)-5-fluoro-N4-[4-(2-hydroxy-1,1-dimethylethyl)phenyl]-pyrimidine-2,4-diamine, N4-[4-(1-ethoxycarbonyl-1-methyl)ethylphenyl]-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine was reduced with DIBALH to give 5-fluoro-N2-[4-(2-hydroxy-1,1-dimethylethyl)phenyl]-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine. ¹H NMR (DMSO-d₆): δ 9.24 (s, 1H), 9.13 (s, 1H), 9.01 (s, 1H), 8.04 (d, 1H, J = 3.5 Hz), 7.68 (d, 2H, J = 8.8 Hz), 7.29 (d, 2H, J = 8.8 Hz),

7.16 (br s, 1H), 7.07 (m, 1H), 6.94 (t, 1H, 8.8 Hz), 6.30 (m, 1H), 4.64 (t, 1H, J= 5.8 Hz), 3.38 (d, 2H, J= 5.3 Hz), 1.20 (s, 6H); LCMS: ret. time: 17.36 min.; purity: 100%; MS (*m/e*): 369 (MH⁺).

5 **7.3.640 (R935174): 5-Fluoro-N2-[4-(2-hydroxyethoxy)phenyl]-N4-(2-hydroxymethylbenzofur-5-yl)-2,4-pyrimidinediamine**

In like manner to the preparation of N2-(3,4-ethylenedioxyphenyl)-5-fluoro-N4-[4(2-hydroxy-1,1-dimethylethyl)phenyl]-2,4-pyrimidinediamine, N2-(2-carbomethoxybenzofur-5-yl)-5-fluoro-N4-(4-methoxycarbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine was reduced with DIBALH to provide 5-fluoro-N2[4-(2-hydroxyethoxy)phenyl]-N2-(2-hydroxymethylbenzofur-5-yl)-2,4-pyrimidinediamine. ¹H NMR (DMSO-d₆): δ 9.26 (s, 1H), 8.94 (s, 1H), 8.01 (d, 1H, J= 4.1 H), 7.99 (s, 1H), 7.52-7.45 (m, 4H), 6.72 (d, 2H, J= 9.3 Hz), 6.66 (s, 1H), 5.46 (t, 1H, J= 5.3 Hz), 4.82 (t, 1H, J= 5.8 Hz), 4.55 (d, 2H, J= 5.8 Hz), 3.89 (t, 2H, J= 5.3 Hz), 3.67 (app qt, 2H, J= 5.3 Hz); LCMS: ret. time: 14.97 min.; purity: 91%; MS (*m/e*): 411 (MH⁺).

15 **7.3.641 (R935176): N2-(3,4-Ethylenedioxyphenyl)-5-fluoro-N4-[3-(2-hydroxyethoxy)phenyl]-2,4-pyrimidinediamine:**

In like manner to the preparation of N2-(3,4-ethylenedioxyphenyl)-5-fluoro-N4-[4-(2-hydroxy-1,1-dimethylethyl)phenyl]-2,4-pyrimidinediamine, N2-(3,4-ethylenedioxyphenyl)-5-fluoro-N4-(3-methoxycarbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine was reduced with DIBALH to provide N2-(3,4-ethylenedioxyphenyl)-5-fluoro-N4-[3-(2-hydroxyethoxy)phenyl]-2,4-pyrimidinediamine. ¹H NMR (DMSO-d₆): δ 9.22 (s, 1H), 8.98 (s, 1H), 8.05 (d, 1H, J= 3.5 Hz), 7.47 (dd, 1H, J= 1.1 and 8.2 Hz), 7.27 (t, 1H, J= 1.7 Hz), 7.23 (d, 1H, J= 2.3 Hz), 7.18 (t, 1H, J= 8.2 Hz), 7.05 (dd, 1H, J= 2.3 and 8.8 Hz), 6.68 (d, 1H, J= 8.2 Hz), 6.61 (dd, 1H, J= 1.7 and 8.8 Hz), 4.85 (t, 1H, J= 5.3 Hz), 4.18-4.14 (m, 4H), 3.91 (t, 2H, J= 5.3 Hz), 3.68 (qt, 2H, J= 5.3 Hz); LCMS: ret. time: 17.35 min.; purity: 92%; MS (*m/e*): 399 (MH⁺).

25 **7.3.642 (R935177): 5-Fluoro-N2-[4-(2-hydroxy-1,1-dimethylethyl)phenyl]-N4-(2-hydroxymethylbenzofur-5-yl)-2,4-pyrimidinediamine**

30 In like manner to the preparation of N2-(3,4-ethylenedioxyphenyl)-5-fluoro-N4-[4-(2-hydroxy-1,1-dimethylethyl)phenyl]-2,4-pyrimidinediamine, N4-(2-carbomethoxybenzofur-5-yl)-N2-[4-(1-ethoxycarbonyl-1-methyl)ethylphenyl]-5-fluoro-2,4-

pyrimidinediamine was reduced with DIBALH to produce 5-fluoro- N2-[4-(2-hydroxy-1,1-dimethylethyl)phenyl]-N4-(2-hydroxymethylbenzofur-5-yl)-2,4-pyrimidinediamine. LCMS: ret. time: 18.17 min.; purity: 94%; MS (*m/e*): 423 (MH⁺).

7.3.643 (R935178): 5-Fluoro-N2-[3-(2-hydroxyethoxy)phenyl]-N4-(2-hydroxymethylbenzofur-5-yl)-2,4-pyrimidinediamine

In like manner to the preparation of N2-(3,4-ethylenedioxyphenyl)-5-fluoro-N4-[4-(2-hydroxy-1,1-dimethylethyl)phenyl]-2,4-pyrimidinediamine, N4-(2-carbomethoxybenzofur-5-yl)-5-fluoro-N2-(3-methoxycarbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine was reduced with DIBALH to provide 5-fluoro-N2-[3-(2-hydroxyethoxy)phenyl]-N4-(2-hydroxymethylbenzofur-5-yl)-2,4-pyrimidinediamine. ¹H NMR (DMSO-d₆): δ 9.93 (s, 1H), 9.12 (s, 1H), 8.07 (d, 1H, J= 3.6 Hz), 8.01 (d, 1H, J= 2.3 Hz), 7.55-7.46 (m, 2H), 7.29 (br s, 1H), 7.23 (d, 1H, J= 8.2 Hz), 7.03 (t, 1H, J= 8.2 Hz), 6.68 (s, 1H), 6.44 (dd, 1H, J= 2.3 and 8.2 Hz), 5.47 (t, 1H, J= 5.8 Hz), 4.80 (t, 1H, J= 5.3 Hz), 4.55 (d, 2H, J= 5.3 Hz), 3.81 (qt, 2H, J= 5.3 Hz), 3.63 (qt, 2H, J= 5.3 Hz); LCMS: ret. time: 15.41 min.; purity: 88%; MS (*m/e*): 411 (MH⁺).

7.3.644 (R935181): N4-(3,5-Dimethoxyphenyl)-5-fluoro-N2-[3-(2-hydroxyethoxy)phenyl]-2,4-pyrimidinediamine

In like manner to the preparation of N2-(3,4-ethylenedioxyphenyl)-5-fluoro-N4-[4-(2-hydroxy-1,1-dimethylethyl)phenyl]-2,4-pyrimidinediamine, N4-(3,5-dimethoxyphenyl)-5-fluoro-N2-(3-methoxycarbonylmethyleneoxyphenyl)-2,4-pyrimidineamine was reduced with DIBALH to give N4-(3,5-dimethoxyphenyl)-5-fluoro-N2-[3-(2-hydroxyethoxy)phenyl]-2,4-pyrimidinediamine: ¹H NMR (DMSO-d₆): δ 9.24 (s, 1H), 9.18 (s, 1H), 8.11 (d, 1H, J= 3.5 Hz), 7.31-7.26 (m, 2H), 7.05 (d, 1H, J= 8.2 Hz), 6.99 (d, 1H, J= 2.3 Hz), 6.43 (dd, 1H, J= 2.3 Hz, 8.2 Hz), 6.20 (t, 1H, J= 2.3 Hz), 4.80 (t, 1H, J= 5.8 Hz), 3.83 (t, 2H, J= 5.3 Hz), 3.67 (s, 6H), 3.66-3.60 (m, 2H); LCMS: ret. time: 18.78 min.; purity: 95%; MS (*m/e*): 400 (MH⁺).

7.3.645 (R935183): 5-Fluoro-N2-[4-(2-hydroxyethoxy)phenyl]-N4-(3,4-propylenedioxyphenyl)-2,4-pyrimidinediamine

In like manner to the preparation of N2-(3,4-ethylenedioxyphenyl)-5-fluoro-N4-[4-(2-hydroxy-1,1-dimethylethyl)phenyl]-2,4-pyrimidinediamine, 5-fluoro-N2-[4-(methoxycarbonylmethyleneoxy)phenyl]-N4-(3,4-propylenedioxyphenyl)-2,4-pyrimidinediamine was reduced with DIBAL-H to provide 5-fluoro-N2-[4-(2-

hydroxyethoxy)phenyl]-N4-(3,4-propylenedioxyphenyl)-2,4-pyrimidinediamine. ¹H NMR (DMSO-d₆): δ 9.15 (s, 1H), 8.97 (s, 1H), 8.00 (d, 1H, J= 3.5 Hz), 7.49 (d, 2H; J= 8.8 Hz), 7.40-7.31 (m 2H), 6.88 (d, 1H, J= 8.8 Hz), 6.80 (d, 2H, J= 8.8 Hz), 4.82 (t, 1H, J= 5.3 Hz), 4.12-4.04 (m 4H), 3.90 (t, 2H, J= 5.2 Hz), 3.70-3.65 (app qt, 2H, J= 5.3 Hz), 2.07 (q, 2H, J= 5.3 Hz); LCMS: ret. time: 17.05 min.; purity: 96%; MS (*m/e*): 413 (MH⁺).

7.3.646 (R935186): 5-Fluoro-N2-[4-(2-hydroxyethoxy)phenyl]-N4-(3,4-propylenedioxyphenyl)-2,4-pyrimidinediamine

In like manner to the preparation of N2-(3,4-ethylenedioxyphenyl)-5-fluoro-N4-[4(2-hydroxy-1,1-dimethylethyl)phenyl]-2,4-pyrimidinediamine, 5-fluoro-N2-[3-(methoxycarbonylmethyleneoxy)phenyl]-N4-(3,4-propylenedioxyphenyl)-2,4-pyrimidinediamine was reduced with DIBALH to provide 5-fluoro-N2-[3-(2-hydroxyethoxy)phenyl]-N4-(3,4-propylenedioxyphenyl)-2,4-pyrimidinediamine. ¹H NMR (DMSO-d₆): δ 9.21 (s, 1H), 9.14 (s, 1H), 8.07 (d, 1H, J= 3.5 Hz), 7.42-7.36 (m, 2H), 7.29-7.24 (m, 2H), 7.07 (t, 1H, J= 8.2 Hz), 6.90 (d, 1H, J= 8.8 Hz), 6.45 (dd, 1H, J= 1.7 and 8.3 Hz), 4.82 (t, 1H, J= 5.3 Hz), 4.12-4.04 (app q, 2H, J= 5.3 Hz), 3.86 (t, 2H, J= 5.3 Hz), 3.67 (app qt, 2H, J= 5.3 Hz), 2.07 (q, 2H, J= 5.3 Hz); LCMS: ret. time: 17.95 min.; purity: 96%; MS (*m/e*): 413 (MH⁺).

7.3.647 N4-(4-*tert*-Butylphenyl)-5-fluoro-N2-[2,3-dihydro-2-(carboxy)benzofuran-5-yl]-2,4-pyrimidinediamine (R926720)

The reaction of N2-(4-*tert*-butylphenyl)-5-fluoro-N2-[2,3-dihydro-2-(methoxycarbonyl)benzofuran-5-yl]-2,4-pyrimidinediamine and lithium hydroxide (LiOH) in THF:H₂O at room temperature gave N4-(4-*tert*-butylphenyl)-5-fluoro-N2-[2,3-dihydro-2-(carboxy)benzofuran-5-yl]-2,4-pyrimidinediamine. ¹H NMR (DMSO-d₆): δ 10.01 (bs, 1H), 9.69 (bs, 1H), 8.13 (d, 1H, J= 4.8 Hz), 7.57 (d, 2H, J= 8.7 Hz), 7.50 (s, 1H), 7.35 (d, 2H, J= 8.1 Hz), 7.13 (d, 1H, J= 8.7 Hz), 6.75 (d, 1H, J= 9.0 Hz), 5.21 (dd, 1H, J= 6.3 and 10.5 Hz), 3.49 (dd, 1H, J= 10.5 and 16.5 Hz), 3.17 (dd, 1H, J= 6.6 and 16.5 Hz), 1.27 (s, 9H); LCMS: ret. time: 22.53 min.; purity: 93 %; MS (*m/e*): 423 (MH⁺).

7.3.648 N4-(4-*tert*-Butylphenyl)-N2-(3-carboxymethyleneoxyphenyl)-5-fluor-2,4-pyrimidinediamine (R926726)

In a manner similar to the preparation of N4-(4-*tert*-butylphenyl)-5-fluoro-N2-[2,3-dihydro-2-(carboxy)benzofuran-5-yl]-2,4-pyrimidinediamine, N4-(4-*tert*-butylphenyl)-5-fluoro-N2-(3-methoxycarbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine and lithium

hydroxide were reacted to yield N4-(4-*tert*-butylphenyl)-5-fluoro-N2-(3-carboxymethyleneoxyphenyl)-2,4-pyrimidinediamine. ¹H NMR (DMSO-d₆): δ 12.88 (bs, 1H), 9.29 (s, 1H), 9.16 (s, 1H), 8.07 (d, 1H, J= 3.3 Hz), 7.68 (d, 2H, J= 8.7 Hz), 7.35-7.31 (m, 3H), 7.26 (d, 1H, J= 8.4 Hz), 7.06 (t, 1H, J= 8.4 Hz), 6.41 (dd, 1H, J= 2.4 and 8.4 Hz), 4.54 (s, 2H), 1.27 (s, 9H); ¹⁹F NMR (DMSO-d₆): - 46463; LCMS: ret. time: 22.94 min.; purity: 97 %; MS (m/e): 411 (MH⁺).

7.3.649 5-Fluoro-N2-[3-(carboxymethyleneoxy)phenyl]- N4-[4-(isopropoxy)phenyl]-2,4-pyrimidinediamine (R926731)

In a manner similar to the preparation of N4-(4-*tert*-butylphenyl)-5-fluoro-N2-[2,3-dihydro-2-(carboxy)benzofuran-5-yl]-2,4-pyrimidinediamine, 5-fluoro-N2-(3-methoxycarbonylmethyleneoxyphenyl)-N4-(4-isopropoxyphenyl)-2,4-pyrimidinediamine and lithium hydroxide were reacted to yield 5-fluoro-N2-(3-carboxymethyleneoxyphenyl)-N4-(4-isopropoxyphenyl)-2,4-pyrimidinediamine. ¹H NMR (DMSO-d₆): δ 6.19 (bs, 1H), 9.01 (s, 1H), 8.02 (d, 1H, J= 3.9 Hz), 7.63 (d, 2H, J= 9.3 Hz), 7.19-7.14 (m, 2H), 6.96 (t, 1H, J= 8.7 Hz), 6.87 (d, 2H, J= 9.6 Hz), 6.28 (dd, 1H, J= 2.45 and 9.0 Hz), 4.56 (2q, 1H, J= 6.6 Hz), 3.94 (s, 2H), 1.24 (d, 6H, J= 6.6 Hz); LCMS: ret. time: 20.13 min.; purity: 100 %; MS (m/e): 413 (MH⁺).

7.3.650 N2,N4-Bis(4-carboxymethyleneoxy)phenyl-5-fluoro-2,4-pyrimidinediamine (R926560)

In a manner similar to the preparation of N4-(4-*tert*-butylphenyl)-5-fluoro-N2-[2,3-dihydro-2-(carboxy)benzofuran-5-yl]-2,4-pyrimidinediamine, the hydrolysis of N2,N4-bis(4-methoxycarbonylmethyleneoxyphenyl)-5-fluoro-2,4-pyrimidinediamine with LiOH gave N2,N4-bis(4-carboxymethyleneoxy)phenyl-5-fluoro-2,4-pyrimidinediamine. ¹H NMR (CD₃OD): δ 7.86 (bs, 1H), 7.55 (d, 2H, J= 9.0 Hz), 7.32 (bd, 2H, J= 9.3 Hz), 6.95 (m, 4H), 4.66 (s, 2H), ¹⁹F NMR (CDCl₃): - 21852; LCMS: ret. time: 15.16 min.; purity: 77%; MS (m/e): 429 (MH⁺).

7.3.651 N2-(3-Carboxymethyleneoxyphenyl)-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R926483)

In a manner similar to the preparation of N4-(4-*tert*-butylphenyl)-5-fluoro-N2-[2,3-dihydro-2-(carboxy)benzofuran-5-yl]-2,4-pyrimidinediamine, the reaction of N2-(3-ethoxycarbonylmethyleneoxyphenyl)-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-

pyrimidinediamine with LiOH gave N2-(3-carboxymethyleneoxyphenyl)-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine. ¹H NMR (DMSO-d₆): δ 12.90 (s, 1H), 9.20 (s, 2H), 8.05 (d, 1H, J= 1.2 Hz), 7.32-7.21 (m, 3H), 7.08 (t, 1H, J= 8.1 Hz), 6.80 (d, 1H, J= 8.4 Hz), 6.40 (dd, 1H, J= 1.8 and 8.2 Hz), 4.53 (s, 2H), 4.20 (s, 4H); LCMS: ret. time: 18.26 min.; purity: 100%; MS (m/e): 413 (MH⁺).

7.3.652 N2-(3-Carboxymethyleneoxyphenyl)-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine (R945126)

In a manner similar to the preparation of N4-(4-*tert*-butylphenyl)-5-fluoro-N2-[2,3-dihydro-2-(carboxy)benzofuran-5-yl]-2,4-pyrimidinediamine, the reaction of 5-fluoro-N4-(3-hydroxyphenyl)-N2-(3-(methoxycarbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine with LiOH gave N2-(3-carboxymethyleneoxyphenyl)-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine. ¹H NMR (DMSO-d₆): δ 4.55 (s, 2H), 6.43 (dd, J= 2.1, 8.1 Hz, 1H), 6.48 (dd, J= 2.1 and 7.2 Hz, 1H), 7.06-7.13 (m, 3H), 7.28-7.34 (m, 3H), 8.09 (d, J= 3.6 Hz, 1H), 9.22 (br, 1H), 9.28 (br, 1H), 9.34 (br, 1H); ¹⁹F NMR (282 MHz, DMSO-d₆): δ -163.85; LCMS: ret. time: 15.88 min.; purity: 100%; MS (m/e): 370.63 (MH⁺).

7.3.653 N2-(4-Carboxymethyleneoxyphenyl)-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R926238)

In a manner similar to the preparation of N4-(4-*tert*-butylphenyl)-5-fluoro-N2-[2,3-dihydro-2-(carboxy)benzofuran-5-yl]-2,4-pyrimidinediamine, the reaction of N2-(4-ethoxycarbonylmethyleneoxyphenyl)-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine with LiOH gave N2-(carboxymethyleneoxyphenyl)-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine. ¹H NMR (DMSO-d₆): δ 8.16 (d, 1H, J= 4.8 Hz), 7.37 (bd, 2H, J= 9 Hz), 7.25 (d, 1H, J= 3 Hz), 7.08 (m, 1H), 6.83 (m, 3H), 4.64 (s, 2H), 4.23 (s, 4H); LCMS: ret. time: 19.15 min.; purity: 100%; MS (m/e): 413 (MH⁺).

7.3.654 N2-(4-Carboxymethyleneoxyphenyl)-5-Fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine (R926564)

In a manner similar to the preparation of N4-(4-*tert*-butylphenyl)-5-fluoro-N2-[2,3-dihydro-2-(carboxy)benzofuran-5-yl]-2,4-pyrimidinediamine, 5-fluoro-N2-(4-ethoxycarbonylmethyleneoxyphenyl)-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine upon treatment with LiOH gave 5-fluoro-N2-(4-carboxymethyleneoxyphenyl)-N4-(3-

hydroxyphenyl)-2,4-pyrimidinediamine. ^1H NMR (CD_3OD): δ 7.89 (d, 1H, $J=5.1$ Hz), 7.34 (dd, 2H, $J=2.1$ and 9.3 Hz), 7.19-7.08 (m, 2H), 6.98 (dd, 2H, $J=2.4$ and 8.4 Hz), 6.69 (m, 1H), 4.68 (s, 2H); ^{19}F NMR (CD_3OD): -21860; LCMS: ret. time: 15.69 min.; purity: 99%; MS (m/e): 371 (MH^+).

5 **7.3.655 N2-(2-Carboxybenzofuran-5-yl)-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine (R926478)**

In a manner similar to the preparation of N4-(4-*tert*-butylphenyl)-5-fluoro-N2-[2,3-dihydro-2-(carboxy)benzofuran-5-yl]-2,4-pyrimidinediamine, 5-fluoro-N4-(3-hydroxyphenyl)-N2-(2-methoxycarbonylbenzofuran-5-yl)-4-pyrimidinediamine upon LiOH
10 treatment gave N2-(2-carboxybenzofuran-5-yl)-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine. ^1H NMR (CD_3OD): δ 7.97 (bd, 2H), 7.60-7.44 (m, 4H), 7.20-7.05 (m, 3H), 6.69 (bd, 1H); ^{19}F NMR (CD_3OD): -21844; LCMS: ret. time: 16.77 min.; purity: 100%; MS (m/e): 381 (MH^+).

15 **7.3.656 N2-(2-Carboxyindol-5-yl)-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine (R926479)**

In a manner similar to the preparation of N4-(4-*tert*-butylphenyl)-5-fluoro-N2-[2,3-dihydro-2-(carboxy)benzofuran-5-yl]-2,4-pyrimidinediamine, N2-(2-ethoxycarbonylindol-5-yl)-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine upon LiOH treatment gave
20 N2-(2-carboxyindol-5-yl)-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine. ^1H NMR (CD_3OD): δ 7.83 (m, 1H), 7.73 (s, 1H), 7.50 (bd, 1H, $J=8.7$ Hz), 7.30-7.11 (m, 5H), 6.68 (bd, 1H); LCMS: ret. time: 16.50 min.; purity: 97%; MS (m/e): 380 (MH^+).

7.3.657 N4-(4-*tert*-Butylphenyl)-N2-(2-carboxybenzofuran-5-yl)-5-fluoro-2,4-pyrimidinediamine (R926481)

In a manner similar to the preparation of N4-(4-*tert*-butylphenyl)-5-fluoro-N2-[2,3-dihydro-2-(carboxy)benzofuran-5-yl]-2,4-pyrimidinediamine, LiOH treatment with N4-(4-*tert*-butylphenyl)-5-fluoro-N2-(2-methoxycarbonylbenzofuran-5-yl)-2,4-pyrimidinediamine
25 gave N4-(4-*tert*-butylphenyl)-N2-(2-carboxybenzofuran-5-yl)-5-fluoro-2,4-pyrimidinediamine. ^1H NMR (CD_3OD): δ 9.3 (bd, 2H), 8.25 (s, 1H), 8.10 (s, 1H), 7.65-7.30 (m, 5H), 1.25 (s, 9H); ^{19}F NMR (CD_3OD): -21844; LCMS: ret. time: 23.32 min.;
30 purity: 100%; MS (m/e): 421 (MH^+).

7.3.658 N4-(3-*tert*-Butylphenyl)-N2-[3-carboxymethyleneoxyphenyl]-5-fluoro-2,4-pyrimidinediamine R940280

In a manner similar to the preparation of N4-(4-*tert*-butylphenyl)-5-fluoro-N2-[2,3-dihydro-2-(carboxy)benzofuran-5-yl]-2,4-pyrimidinediamine, N4-(3-*tert*-butylphenyl)-5-fluoro-N2-(3-methoxycarbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine was reacted with LiOH to give N4-(3-*tert*-butylphenyl)-N2-(3-carboxymethyleneoxyphenyl)-5-fluoro-2,4-pyrimidinediamine. LCMS: ret. time: 23.61 min.; purity: 99 %; MS (m/e): 410 (M⁺), 412 (MH⁺); ¹H NMR (DMSO-d₆): δ 9.45 (1H, s), 9.33 (1H, s), 8.21 (1H, d, J= 3.9 Hz), 7.98 (1H, d, J= 6.6 Hz), 7.60 (1H, t, J= 2 Hz), 7.44-7.34 (3H, m), 7.24-7.15 (2H, m), 6.54 (1H, d, J= 7.8 Hz), 4.68 (2H, s), 1.36 (9H, s).

7.3.659 N2-(3-Carboxymethyleneaminophenyl)-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R950190)

The reaction of N2-(3-ethoxycarbonylmethyleneaminophenyl)-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine (0.1 g) and LiOH (10 equivalents) in MeOH:water (1:1, v/v) for 1h at room temperature followed by treatment with aqueous HCl gave the solid. The resulting solid was filtered, washed with water and dried to give N2-(3-carboxymethyleneaminophenyl)-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine. LCMS: ret. time: 18.23 min.; purity: 87.6%; MS (m/e): 412.01 (MH⁺).

7.3.660 N2-(Carboxymethyleneaminophenyl)-5-fluoro-N4-[3-(2-hydroxyethyloxy)phenyl]-2,4-pyrimidinediamine (R950230)

In a manner similar to the preparation of N2-(3-carboxymethyleneaminophenyl)-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine, the hydrolysis of N2-(ethoxycarbonylmethyleneaminophenyl)-5-fluoro-N4-[3-(2-hydroxyethylenoxy)phenyl]-2,4-pyrimidinediamine with LiOH gave N2-(carboxymethyleneaminophenyl)-5-fluoro-N4-[3-(2-hydroxyethyloxy)phenyl]-2,4-pyrimidinediamine. LCMS: ret. time: 12.15 min.; purity: 78.3%; MS (m/e): 413.01 (MH⁺).

7.3.661 5-Fluoro-N4-[3-(2-hydroxyethylamino)phenyl]-N2-[3-[N-(2-hydroxyethylamino)]carbonylmethyleneaminophenyl]-2,4-pyrimidinediamine (R950231)

A mixture of N2-(carboxymethyleneaminophenyl)-5-fluoro-N4-[3-(2-hydroxyethylamino)phenyl]-2,4-pyrimidinediamine (10 mg), 2-aminoethanol (10 equiv.) and PyBroP (2 equiv.) was stirred in 0.5 ml DMF for 24 hours at room temperature. The

mixture was diluted with water, extracted with EtOAc and the organic phase was dried over MgSO₄. The solvent was removed under reduced pressure and the residue was subjected to column chromatography on silica gel (CHCl₃:Acetone, 2:1) to give 5-fluoro-N4-[3-(2-hydroxyethylamino)phenyl]-N2-[3-[N-(2-hydroxyethylamino)]carbonylmethyleneaminophenyl]-2,4-pyrimidinediamine. LCMS: ret. time: 12.98 min.; purity: 92.6%; MS (m/e): 455.97 (MH⁺).

7.3.662 N2-[3-(N-2-Aminoethylamino)carbonylmethyleneaminophenyl]-5-fluoro-N4-[3-(2-hydroxyethylenoxy)phenyl]-2,4-pyrimidinediamine (R950232)

In like manner to the preparation of N4-[3-(2-hydroxyethylamino)phenyl]-N2-[3-[N-(2-hydroxyethylamino)]carbonylmethyleneaminophenyl]-5-fluoro-2,4-pyrimidinediamine, N2-(carboxymethyleneaminophenyl)-5-fluoro-N4-[3-(2-hydroxyethylamino)phenyl]-2,4-pyrimidinediamine and 1,2-ethylenediamine were reacted to afford N2-[3-(N-2-aminoethylamino)carbonylmethyleneaminophenyl]-5-fluoro-N4-[3-(2-hydroxyethylenoxy)phenyl]-2,4-pyrimidinediamine. LCMS: ret. time: 11.31 min.; purity: 93.6%; MS (m/e): 454.94 (MH⁺).

7.3.663 5-Fluoro-N4-[3-(2-hydroxyethylamino)phenyl]-N2-[3-(N-methylamino)carbonylmethyleneaminophenyl]-2,4-pyrimidinediamine (R950233)

In like manner to the preparation of N4-[3-(2-hydroxyethylamino)phenyl]-N2-[3-[N-(2-hydroxyethylamino)]carbonylmethyleneaminophenyl]-5-fluoro-2,4-pyrimidinediamine, N2-(carboxymethyleneaminophenyl)-5-fluoro-N4-[3-(2-hydroxyethylamino)phenyl]-2,4-pyrimidinediamine and methylamine were reacted to give 5-fluoro-N4-[3-(2-hydroxyethylamino)phenyl]-N2-[3-(N-methylamino)carbonylmethyleneaminophenyl]-2,4-pyrimidinediamine. LCMS: ret. time: 14.93 min.; purity: 92.9%; MS (m/e): 426.27 (MH⁺).

7.3.664 5-Fluoro-N4-[3-(2-hydroxyethylamino)phenyl]-N2-[3-[N-(2-methylamino)ethylamino]carbonylmethyleneaminophenyl]-2,4-pyrimidinediamine (R950234)

In like manner to the preparation of N4-[3-(2-hydroxyethylamino)phenyl]-N2-[3-[N-(2-hydroxyethylamino)]carbonylmethyleneaminophenyl]-5-fluoro-2,4-pyrimidinediamine, N2-(carboxymethyleneaminophenyl)-5-fluoro-N4-[3-(2-hydroxyethylamino)phenyl]-2,4-pyrimidinediamine and N-methylethylenediamine were reacted to give 5-fluoro-N4-[3-(2-hydroxyethylamino)phenyl]-N2-[3-[N-(2-methylamino)ethylamino]

carbonylmethyleneaminophenyl]-2,4-pyrimidinediamine. LCMS: ret. time: 11.39 min.; purity: 97.7%; MS (m/e): 468.96 (MH⁺).

7.3.665 N2-[3-[N-(2-N-Benzylamino)ethylamino]carbonylmethyleneaminophenyl]-5-fluoro-N4-[3-(2-hydroxyethylamino)phenyl]-2,4-pyrimidinediamine (R950235)

In like manner to the preparation of N4-[3-(2-hydroxyethylamino)phenyl]-N2-[3-[N-(2-hydroxyethylamino)]carbonylmethyleneaminophenyl]-5-fluoro-2,4-pyrimidinediamine, N2-(carboxymethyleneaminophenyl)-5-fluoro-N4-[3-(2-hydroxyethylamino)phenyl]-2,4-pyrimidinediamine and N-benzylethylenediamine were reacted to give N2-[3-[N-(2-N-benzylamino)ethylamino]carbonylmethyleneaminophenyl]-5-fluoro-N4-[3-(2-hydroxyethylamino)phenyl]-2,4-pyrimidinediamine. LCMS: ret. time: 14.39 min.; purity: 97.3%; MS (m/e): 545.01 (MH⁺).

7.3.666 5-Fluoro-N4-[3-(2-hydroxyethylamino)phenyl]-N2-[3-(N-morpholino)carbonylmethyleneaminophenyl]-2,4-pyrimidinediamine (R950236)

In like manner to the preparation of N4-[3-(2-hydroxyethylamino)phenyl]-N2-[3-[N-(2-hydroxyethylamino)]carbonylmethyleneaminophenyl]-5-fluoro-2,4-pyrimidinediamine, N2-(carboxymethyleneaminophenyl)-5-fluoro-N4-[3-(2-hydroxyethylamino)phenyl]-2,4-pyrimidinediamine and morpholine were reacted to afford 5-fluoro-N4-[3-(2-hydroxyethylamino)phenyl]-N2-[3-(N-morpholino)carbonylmethyleneaminophenyl]-2,4-pyrimidinediamine. LCMS: ret. time: 15.24 min.; purity: 94.6xx%; MS (m/e): 482.40 (MH⁺).

7.3.667 N2-[3-(3-N,N-Dimethylaminopropyl)aminocarbonylmethyleneaminophenyl]-5-fluoro-N4-[3-(2-hydroxyethylamino)phenyl]-2,4-pyrimidinediamine (R950237)

In like manner to the preparation of N4-[3-(2-hydroxyethylamino)phenyl]-N2-[3-[N-(2-hydroxyethylamino)]carbonylmethyleneaminophenyl]-5-fluoro-2,4-pyrimidinediamine, N2-(carboxymethyleneaminophenyl)-5-fluoro-N4-[3-(2-hydroxyethylamino)phenyl]-2,4-pyrimidinediamine and N,N-dimethylpropanediamine were reacted to give N2-[3-(3-N,N-Dimethylaminopropyl)aminocarbonylmethyleneaminophenyl]-5-fluoro-N4-[3-(2-hydroxyethylamino)phenyl]-2,4-pyrimidinediamine. LCMS: ret. time: 13.33 min.; purity: 91.4%; MS (m/e): 497.47 (MH⁺).

7.3.668 N2-[3-[N-(2,3-Dihydroxypropyl)amino]carbonylmethyleneaminophenyl]-5-fluoro-N4-[3-(2-hydroxyethylamino)phenyl]-2,4-pyrimidinediamine (R950238)

5 In like manner to the preparation of N4-[3-(2-hydroxyethylamino)phenyl]-N2-[3-[N-(2-hydroxyethylamino)]carbonylmethyleneaminophenyl]-5-fluoro-2,4-pyrimidinediamine, N2-(carboxymethyleneaminophenyl)-5-fluoro-N4-[3-(2-hydroxyethylamino)phenyl]-2,4-pyrimidinediamine and 1-amino-2,3-propanediol were reacted to give N2-[3-[N-(2,3-dihydroxypropyl)amino]carbonylmethyleneaminophenyl]-5-fluoro-N4-[3-(2-hydroxyethylamino)phenyl]-2,4-pyrimidinediamine. LCMS: ret. time: 12.86 min.; purity: 90.0%; MS (m/e): 486.40 (MH⁺).

7.3.669 5-Fluoro-N4-[3-(2-hydroxyethylamino)phenyl]-N2-[3-(N-morpholinoethyleneamino)carbonylmethyleneaminophenyl]-2,4-pyrimidinediamine (R950239)

15 In like manner to the preparation of N4-[3-(2-hydroxyethylamino)phenyl]-N2-[3-[N-(2-hydroxyethylamino)]carbonylmethyleneaminophenyl]-5-fluoro-2,4-pyrimidinediamine, N2-(carboxymethyleneaminophenyl)-5-fluoro-N4-[3-(2-hydroxyethylamino)phenyl]-2,4-pyrimidinediamine and 4-(2-aminoethyl)morpholine were reacted to give 5-fluoro-N4-[3-(2-hydroxyethylamino)phenyl]-N2-[3-(N-morpholinoethyleneamino)carbonylmethyleneaminophenyl]-2,4-pyrimidinediamine. LCMS: ret. time: 13.52 min.; purity: 92.4%; MS (m/e): 525.47 (MH⁺).

7.3.670 2,4-Bis[N-(L)-tyrosine methyl ester]-5-ethoxycarbonylpyrimidine (R926514)

and

25 **5-Ethoxycarbonyl-2-methoxy-4-[N-(L)-tyrosine methyl ester]pyrimidine (R926513)**

A mixture of tyrosine methyl ester (58 mg, 0.3 mmol), 2,4-dichloro-5-ethoxycarbonylpyrimidine (44 mg, 0.1 mmol) in MeOH (2mL) was heated in a sealed tube at 100 °C for a period of overnight, diluted with H₂O (20 mL), acidified with 2N HCl and extracted with ethyl acetate (3 x 25 mL). The solvent was evaporated and the residue was purified by preparative TLC using 30% EtOAc/Hexanes to obtain a mixture of 2,4-bis[N-(L)-tyrosine methyl ester]-5-ethoxycarbonylpyrimidine (R926514). ¹H NMR (CDCl₃): δ

8.60 (1H, J= 6.6 Hz), 8.36 (s, 1H), 7.05 (d, 2H, J= 8.7 Hz), 6.84 (d, 2H, J= 8.1 Hz), 6.74 (d, 2H, J= 9 Hz), 6.54 (d, 2H, J= 9 Hz), 4.82 (t, 2H, J= 6 Hz), 4.25 (q, 2H, J= 6.3 Hz), 3.73 (s, 3H), 3.72 (s, 3H), 3.06 (m, 4H), 1.31 (t, 3H, J= 7.2 Hz) and 5-ethoxycarbonyl-2-methoxy-4-[N-(L)-tyrosine methyl ester]pyrimidine (**R926513**): ^1H NMR (CDCl_3): δ 8.78 (s, 1H), 8.65 (d, 1H, J= 6.9 Hz), 7.02 (dd, 2H, J= 2.1 and 6.3 Hz), 6.77 (dd, 2H, J= 2.4 and 6.6 Hz), 4.93 (q, 1H, J= 1.5 and 6.9 Hz), 4.30 (q, 2H, J= 8.1 Hz), 3.90 (s, 3H), 3.70 (s, 3H), 3.17 (dd, 1H, J= 5.4 Hz), 3.06 (dd, 1H, J= 7.5 and 7.8 Hz), 1.33 (t, 3H, J= 6.9 Hz); LCMS: ret. time: 22.58 min.; purity: 99%; MS (m/e): 376 (M^+).

7.3.671 N2,N4-Bis(3,4-ethylenedioxyphenyl)-5-ethoxycarbonyl-2,4-pyrimidinediamine (R926252)

In like manner to the preparation of N2,N4-bis[N-(L)-tyrosine methyl ester]-5-ethoxycarbonylpyrimidine, the reaction of 2,4-dichloro-5-ethoxycarbonylpyrimidine with 3,4-ethylenedioxyaniline gave N2,N4-bis(3,4-ethylenedioxyphenyl)-5-ethoxycarbonyl-2,4-pyrimidinediamine. ^1H NMR ($\text{DMSO}-d_6$): δ 10.01 (s, 1H), 9.65 (bs, 1H), 8.62 (s, 1H), 7.18 (bs, 2H), 7.04 (dd, 1H, J= 1.8 and 8.7 Hz), 6.93 (d, 1H, J= 7.5 Hz), 6.76 (d, 1H, J= 8.7 Hz), 6.65 (d, 1H, J= 8.7 Hz), 4.28 (q, 2H, J= 6.9 Hz), 1.31 (t, 3H, J= 7.2 Hz); LCMS: ret. time: 27.25 min.; purity: 100%; MS (m/e): 451 (MH^+).

7.3.672 N2,N4-Bis(4-methoxycarbonylmethyleneoxyphenyl)-5-ethoxycarbonyl-2,4-pyrimidinediamine (R926253)

In like manner to the preparation of N2,N4-bis[N-(L)-tyrosine methyl ester]-5-ethoxycarbonylpyrimidine, the reaction of 2,4-dichloro-5-ethoxycarbonylpyrimidine with ethyl 4-aminophenoxyacetate gave N2,N4-bis(4-methoxycarbonylmethyleneoxyphenyl)-5-ethoxycarbonyl-2,4-pyrimidinediamine (**R926253**). ^1H NMR (CD_3OD): δ 8.60 (bs, 1H), 7.4 (bs, 1H), 7.33 (d, 4H, J= 9Hz), 6.94 (bd, 4H), 4.76 (s, 2H), 4.75 (s, 2H), 4.44 (q, 2H, J= 6.9 Hz), 3.79 (s, 3H), 1.40 (t, 3H, J= 6.9 Hz); LCMS: ret. time: 25.83 min.; purity: 89%; MS (m/e): 511 (MH^+).

7.3.673 2,4-Bis[N-(L)-phenylalaninyl ethyl ester]-5-ethoxycarbonylpyrimidine (R926526)

In like manner to the preparation of N2,N4-bis[N-(L)-tyrosine methyl ester]-5-ethoxycarbonylpyrimidine, the reaction of 2,4-dichloro-5-ethoxycarbonylpyrimidine with ethyl (L)-phenylalanine ethyl ester in MeOH or EtOAc gave 2,4-bis[N-(L)-phenylalanine ethyl ester]-5-ethoxycarbonylpyrimidine. ^1H NMR (CDCl_3): δ 8.55 (d, 1H, J= 7.2 Hz), 8.51

(s, 1H), 7.35-7.10 (m, 10H), 5.88 (d, 1H, J= 6 Hz), 4.88 (ddd, 1H, J= 6.3 Hz), 4.80 (ddd, 1H, J= 6.3 Hz), 4.23 (q, 2H, J= 7.2 Hz), 4.12 (q, 4H, J= 7.2 Hz), 3.65 (t, 2H, J= 6 Hz), 3.56 (t, 2H, J= 6.0 Hz), 1.30 (t, 2H, J= 6 Hz), 1.30 (t, 3H, J= 7.2 Hz), 1.20 (m, 6H); LCMS: ret. time: 32.22 min.; purity: 89%; MS (m/e): 535 (MH⁺).

5 **7.3.674 2,4-Bis[N-(L)-valinyl ethyl ester]-5-ethoxycarbonylpyrimidine (R926527)**

In like manner to the preparation of N2,N4-bis[N-(L)-tyrosine methyl ester]-5-ethoxycarbonylpyrimidine, the reaction of 2,4-dichloro-5-ethoxycarbonylpyrimidine with ethyl (L)-valine ethyl ester in MeOH or EtOAc gave 2,4-bis[N-(L)-valinyl ethyl ester]-5-ethoxycarbonylpyrimidine. ¹H NMR (CDCl₃): δ 8.59 (d, 1H, J= 7.8 Hz), 8.56 (s, 1H), 5.69 (d, 1H, J= 8.7 Hz), 4.62 (m, 1H), 4.51 (m, 1H), 4.25 (q, 2H, J= 7.5 Hz), 4.20 (m, 4H), 2.20 (m, 2H), 1.34 (t, 3H, J= 7.8 Hz), 1.27 (t, 6H, J= 7.5 Hz), 1.00 (m, 12H); LCMS: ret. time: 29.27 min.; purity: 97%; MS (m/e): 439 (MH⁺).

15 **7.3.675 5-Ethoxycarbonyl-N2-(3-hydroxyphenyl)-4-[N-(L)-phenylalanine ethyl ester]-2-pyrimidineamine (R926528)**

The reaction of 2-chloro-N4-(3-hydroxyphenyl)-5-ethoxycarbonylpyrimidineamine with 3 equivalents of (L)-N-phenylalanine ethyl ester in methanol at 80-100 °C for 24 h followed by dilution with water and acidification with 2N HCl have the acidic solution. The resulting solution was extracted with EtOAc and the residue was purified by silics gel column chromatography to afford 4-[N-(L)-phenylalanine ethyl ester]-N2-(3-hydroxyphenyl)-5-ethoxycarbonyl-2-pyrimidineamine. ¹H NMR (CDCl₃): δ 9.4 (bs, 1H), 9.13 (d, 1H, J= 6 Hz), 8.45 (bs, 1H), 7.59 (s, 1H), 7.34-7.25 (m, 5H), 7.15 (t, 1H, J= 8.1 Hz), 6.73 (bd, 1H, J= 7.5 Hz), 6.67 (dd, 1H, J= 1.8 and 7.8 Hz), 4.86 (dt, 1H, J= 3 and 5.1 Hz), 4.32 (q, 2H, J= 6.3 Hz), 4.19 (q, 2H, J= 7.2 Hz), 3.30 (dd, 1H, J= 4.8 and 8.7 Hz), 3.18 (dd, 1H, J= 5.1 and 8.7 Hz), 1.36 (t, 3H, J= 6.9 Hz), 1.65 (t, 3H, J= 7.2 Hz); LCMS: ret. time: 27.49 min.; purity: 91%; MS (m/e): 451 (MH⁺).

7.3.676 N2-(3,4-Ethylenedioxyphenyl)-5-ethoxycarbonyl-4-[N-(L)-phenyl glycyl ethyl ester]-2-pyrimidineamine (R926536)

In like manner to the preparation of 4-[N-(L)-phenylalanine ethyl ester]-N2-(3-hydroxyphenyl)-5-ethoxycarbonyl-2-pyrimidineamine, the reaction of 2-chloro-5-ethoxycarbonyl-4-[N-(L)-phenyl glycyl ethyl ester]pyrimidine with 3,4-ethylenedioxyaniline in MeOH or EtOAc gave N2-(3,4-ethylenedioxyphenyl)-5-

ethoxycarbonyl-4-[N-(L)-phenyl glyciny ethyl ester]-2-pyrimidineamine. ^1H NMR (CDCl_3): δ 9.15 (s, 1H), 8.9 (s, 1H), 8.61 (s, 1H), 7.48 (m, 2H), 7.38 (m, 3H), 7.16 (bs, 1H), 6.80 (m, 2H), 5.75 (d, 1H), 4.24 (m, 6H), 3.66 (s, 3H), 1.35 (t, 3H); LCMS: ret. time: 28.16 min.; purity: 85%; MS (m/e): 465 (MH^+).

5 **7.3.677 N4-(4-tert-Butoxycarbonylmethyleneoxyphenyl)-5-ethoxycarbonyl-N2-(4-methoxycarbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine (R926579)**

10 In like manner to the preparation of 4-[N-(L)-phenylalanine ethyl ester]-N2-(3-hydroxyphenyl)-5-ethoxycarbonyl-2-pyrimidineamine, the reaction of N4-(4-tert-butoxycarbonylmethyleneoxyphenyl)-2-chloro-5-ethoxycarbonyl-4-pyrimidineamine with methyl 4-aminophenoxyacetate gave N4-(4-tert-butoxycarbonylmethyleneoxyphenyl)-5-ethoxycarbonyl-N2-(4-methoxycarbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine. ^1H NMR (CDCl_3): δ 10.17 (s, 1H), 8.73 (s, 1H), 8.45 (bs, 1H), 7.49 (d, 2H, $J=8.7$ Hz), 7.43 (d, 15 2H, $J=8.7$ Hz), 7.33 (bs, 1H), 6.87 (d, 2H, $J=6$ Hz), 6.84 (d, 2H, $J=5.7$ Hz), 4.63 (s, 2H), 4.53 (s, 2H), 4.33 (q, 2H, $J=6.9$ Hz), 3.81 (s, 3H), 1.49 (s, 9H), 1.39 (t, 3H, $J=7.5$ Hz); LCMS: ret. time: 27.93 min.; purity: 96%; MS (m/e): 553 (MH^+).

20 **7.3.678 N4-(4-tert-Butoxycarbonylmethyleneoxyphenyl)-N2-(4-methoxycarbonylmethyleneoxyphenyl)-5-methoxycarbonyl-2,4-pyrimidinediamine (R926580)**

25 In like manner to the preparation of 4-[N-(L)-phenylalanine ethyl ester]-N2-(3-hydroxyphenyl)-5-ethoxycarbonyl-2-pyrimidineamine, the reaction of N4-(4-tert-butoxycarbonylmethyleneoxyphenyl)-2-chloro-5-ethoxycarbonyl-4-pyrimidineamine with methyl 4-aminophenoxyacetate gave N4-(4-tert-butoxycarbonylmethyleneoxyphenyl)-5-methoxycarbonyl-N2-(4-methoxycarbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine. 5-methyl ester was obtained due to the cross esterification reaction in MeOH. ^1H NMR (CDCl_3): δ 10.13 (s, 1H), 8.73 (s, 1H), 8.45 (bs, 1H), 7.49 (d, 2H, $J=8.7$ Hz), 7.43 (d, 2H, $J=8.7$ Hz), 7.33 (bs, 1H), 6.87 (m, 4H), 4.63 (s, 2H), 4.53 (s, 2H), 4.33 (q, 2H, $J=6.9$ Hz), 3.88 (s, 3H), 3.81 (s, 3H), 1.49 (s, 9H); LCMS: ret. time: 27.43 min.; purity: 100%; MS 30 (m/e): 539 (MH^+).

7.3.679 N4-(4-Carboxymethyleneoxyphenyl)-5-ethoxycarbonyl-N2-(4-methoxycarbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine (R926583)

The treatment of N4-(4-tert-butoxycarbonylmethyleneoxyphenyl)-5-ethoxycarbonyl-N2-(4-methoxycarbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine with trifluoroacetic acid in THF:H₂O at room temperature afforded N4-(4-carboxymethyleneoxyphenyl)-5-ethoxycarbonyl-N2-(4-methoxycarbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine. ¹H NMR (DMSO-d₆): δ 10.03 (s, 1H), 8.65 (s, 1H), 7.49 (bd, 4H, J= 8.7 Hz), 6.89 (d, 2H, J= 9.3 Hz), 6.81 (d, 2H, J= 8.1 Hz), 4.70 (s, 2H), 4.65 (s, 2H), 4.33 (q, 2H, J= 6.9 Hz), 3.81 (s, 3H), 1.49 (s, 9H), 1.39 (t, 3H, J= 7.5 Hz); LCMS: ret. time: 22.28 min.; purity: 73%; MS (m/e): 497 (MH⁺).

7.3.680 N2-(4-Carboxymethyleneoxyphenyl)-5-ethoxycarbonyl-N4-(4-methoxycarbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine (R926584)

The treatment of N2-(4-tert-butoxycarbonylmethyleneoxyphenyl)-5-ethoxycarbonyl-N4-(4-methoxycarbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine with trifluoroacetic acid in THF:H₂O at room temperature afforded N2-(4-carboxymethyleneoxyphenyl)-5-ethoxycarbonyl-N4-(4-methoxycarbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine. ¹H NMR (DMSO-d₆): δ 10.01 (s, 1H), 8.64 (s, 1H), 7.45 (bd, 4H, J= 7.2 Hz), 6.90 (d, 2H, J= 8.7 Hz), 6.75 (d, 2H, J= 8.4 Hz), 4.80 (s, 2H), 4.38 (s, 2H), 4.26 (q, 2H, J= 7.2 Hz), 3.70 (s, 3H), 1.30 (t, 3H, J= 7.2 Hz); LCMS: ret. time: 22.37 min.; purity: 100%; MS (m/e): 497 (MH⁺).

7.3.681 5-Carboxy-N2-(3-hydroxyphenyl)-N4-[N-(L)-phenylglycine]-2-pyrimidineamine (R926535)

The LiOH hydrolysis of N2-(3-hydroxyphenyl)-5-ethoxycarbonyl-4-[N-(L)-phenylglycine ethyl ester]-2-pyrimidineamine afforded 5-carboxy-N2-(3-hydroxyphenyl)-N4-[N-(L)-phenylglycine]-2-pyrimidineamine. ¹H NMR (CD₃OD): δ 8.89 (s, 1H), 8.50 (s, 1H), 7.43 (m, 2H), 7.33 (m, 3H), 7.14 (m, 2H), 6.98 (m, 2H), 6.62 (m, 1H), 5.71 (s, 1H); LCMS: ret. time: 17.75 min.; purity: 73%; MS (m/e): 382 (MH⁺).

7.3.682 5-Amino-6-ethoxycarbonyl-N2,N4-bis(3-hydroxyphenyl)-2,4-pyrimidinediamine (R925856)

A suspension of 6-ethoxycarbonyl-N2,N4-bis(3-hydroxyphenyl)-5-nitro-2,4-pyrimidinediamine and 10% Pd/C (10% by weight) in ethanol was prepared and reacted in

a Parr bottle under hydrogen gas (20 PSI) for 1h. The reaction mixture was filtered through Celite. Purification by column chromatography gave 5-amino-6-ethoxycarbonyl-N2,N4-bis(3-hydroxyphenyl)-2,4-pyrimidinediamine. ¹H NMR (CD₃OD): δ 7.30 (bs, 1H), 7.18-7.10 (m, 3H), 7.00 (t, 2H, J= 8.1 Hz), 6.59-6.54 (m, 1H), 6.33 (dd, 1H, J= 2.1 and 11.1 Hz), 4.39 (q, 2H, J= 6.9 Hz), 1.43 (t, 3H, J= 6.9 Hz); LCMS: ret. time: 19.24 min.; purity: 100 %; MS (m/e): 382 (MH⁺).

7.3.683 5-Amino-6-ethoxycarbonyl-N2,N4-bis(3,4-ethylenedioxyphenyl)-2,4-pyrimidinediamine (R925857)

In a manner similar to the preparation of 5-amino-6-ethoxycarbonyl-N2,N4-bis(3-hydroxyphenyl)-2,4-pyrimidinediamine, 6-ethoxycarbonyl-N2,N4-bis(3,4-ethylenedioxyphenyl)-5-nitro-2,4-pyrimidinediamine, hydrogen, and 10% Pd/C were reacted to yield 5-amino-6-ethoxycarbonyl-N2,N4-bis(3,4-ethylenedioxyphenyl)-2,4-pyrimidinediamine. ¹H NMR (CD₃OD): δ 7.16 (d, 1H, J= 2.4 Hz), 7.07 (d, 1H, J= 2.4 Hz), 7.04 (dd, 1H, J= 2.4 and 9.0 Hz), 6.84-6.79 (m, 2H), 6.70 (d, 1H, J= 9.0), 4.43 (q, 2H, J= 7.8 Hz), 4.25 (s, 4H), 4.21 (bs, 4H), 1.43 (t, 3H, J= 7.8 Hz); LCMS: ret. time: 23.70 min.; purity: 100 %; MS (m/e): 466 (MH⁺).

7.3.684 5-Amino-N2,N4-bis(ethoxycarbonylmethyl)-6-ethoxycarbonyl-2,4-pyrimidinediamine (R925865)

In a manner similar to the preparation of 5-amino-6-ethoxycarbonyl-N2,N4-bis(3-hydroxyphenyl)-2,4-pyrimidinediamine, 6-ethoxycarbonyl-N2,N4-bis(ethoxycarbonylmethyl)-5-nitro-2,4-pyrimidinediamine, hydrogen, and 10% Pd/C were reacted to yield 5-amino-N2,N4-bis(ethoxycarbonylmethyl)-6-ethoxycarbonyl-2,4-pyrimidinediamine. ¹H NMR (CDCl₃): δ 6.25 (bs, 2H), 4.38 (q, 2H, J= 6.9 Hz), 4.23-4.14 (m, 6H), 4.05 (bs, 2H), 1.39 (t, 3H, J= 6.9 Hz), 1.30-1.22 (m, 6H); LCMS: ret. time: 17.67 min.; purity: 95 %; MS (m/e): 370 (MH⁺).

7.3.685 5-Amino-N2,N4-bis(4-ethoxycarbonylmethylenoxyphenyl)-6-ethoxycarbonyl-2,4-pyrimidinediamine (R926567)

Hydrogenation of N2,N4-bis(4-ethoxycarbonylmethylenoxyphenyl)-6-ethoxycarbonyl-5-nitro-2,4-pyrimidinediamine using Pd/C in MeOH at 40 PSI gave 5-amino-N2,N4-bis(4-ethoxycarbonylmethylenoxyphenyl)-6-ethoxycarbonyl-2,4-pyrimidinediamine. ¹H NMR (CDCl₃): δ 7.47 (d, 2H, J= 8.7 Hz), 7.41 (d, 2H, J= 8.7 Hz), 6.88 (d, 2H, J= 8.1 Hz), 6.81 (d, 2H, J= 8.7 Hz), 4.63 (s, 2H), 4.59 (s, 2H), 4.41 (q, 2H, J=

7.5 Hz), 4.29 (m, 4H), 1.44 (t, 3H), 1.31 (m, 6H); LCMS: ret. time: 26.15 min.; purity: 97%; MS (m/e): 554 (MH⁺).

7.3.686 N2,N4-Bis(4-ethoxycarbonylmethyleneoxyphenyl)-6-ethoxycarbonyl-5-(phenylaminocarbonylamino)-2,4-pyrimidinediamine (R926571)

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A dry reaction flask equipped with a rubber septum and a N₂ inlet was charged with 5-amino-N2,N4-bis(4-ethoxycarbonylmethyleneoxyphenyl)-6-ethoxycarbonyl-2,4-pyrimidinediamine, equimolar amount of pyridine and phenyl isocyanate at room temperature. The reaction was allowed to stirred at room temperature for overnight and the resulting reaction was poured over n-hexane to precipitate the desired product, N2,N4-bis(4-ethoxycarbonylmethyleneoxyphenyl)-6-ethoxycarbonyl-5-(phenylaminocarbonylamino)-2,4-pyrimidinediamine. ¹H NMR (CDCl₃): δ 7.92 (s, 1H), 7.47 (s, 1H), 7.35 (bt, 5H, J= 8.4 Hz), 7.25 (bt, 2H, J= 7.5 Hz), 7.03 (m, 2H), 6.81 (d, 2H, J= 8.7 Hz), 6.76 (d, 2H, J= 8.7 Hz), 4.60 (s, 2H), 4.58 (s, 2H), 4.29 (m, 6H), 1.45 (m, 9H); LCMS: ret. time: 27.75 min.; purity: 91%; MS (m/e): 673 (MH⁺).

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7.3.687 5-Allylaminocarbonylamino-N2,N4-bis(4-ethoxycarbonylmethyleneoxyphenyl)-6-ethoxycarbonyl-2,4-pyrimidinediamine (R926585)

In like manner to the preparation of N2,N4-bis(4-ethoxycarbonylmethyleneoxyphenyl)-6-ethoxycarbonyl-5-(phenylaminocarbonylamino)-2,4-pyrimidinediamine, the reaction of 5-amino-N2,N4-bis(4-ethoxycarbonylmethyleneoxyphenyl)-6-ethoxycarbonyl-2,4-pyrimidinediamine with allyl isocyanate gave 5-allylaminocarbonylamino-N2,N4-bis(4-ethoxycarbonylmethyleneoxyphenyl)-6-ethoxycarbonyl-2,4-pyrimidinediamine. LCMS: ret. time: 25.60 min.; purity: 91%; MS (m/e): 637 (MH⁺).

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7.3.688 N2,N4-Bis(4-ethoxycarbonylmethyleneoxyphenyl)-6-ethoxycarbonyl-5-(ethoxycarbonylaminocarbonylamino)-2,4-5-pyrimidinetriamine (R926586)

In like manner to the preparation of N2,N4-bis(4-ethoxycarbonylmethyleneoxyphenyl)-6-ethoxycarbonyl-5-(phenylaminocarbonylamino)-2,4-pyrimidinediamine, the reaction of 5-amino-N2,N4-bis(4-ethoxycarbonylmethyleneoxyphenyl)-6-ethoxycarbonyl-2,4-pyrimidinediamine with ethoxycarbonyl isocyanate gave N2,N4-bis(4-ethoxycarbonylmethyleneoxyphenyl)-6-ethoxycarbonyl-5-

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(ethoxycarbonylaminocarbonylamino)-2,4-pyrimidinediamine. LCMS: ret. time: 26.79 min.; purity: 88%; MS (m/e): 669 (MH⁺).

7.3.689 N2,N4-Bis(4-ethoxycarbonylmethyleneoxyphenyl)-6-ethoxycarbonyl-5-(ethoxycarbonylmethyleneaminocarbonylamino)-2,4-pyrimidinediamine (R926587)

In like manner to the preparation of N2,N4-bis(4-ethoxycarbonylmethyleneoxyphenyl)-6-ethoxycarbonyl-5-(phenylaminocarbonylamino)-2,4-pyrimidinediamine, the reaction of 5-amino-N2,N4-bis(4-ethoxycarbonylmethyleneoxyphenyl)-6-ethoxycarbonyl-2,4-pyrimidinediamine with ethylacetyl isocyanate gave N2,N4-bis(4-ethoxycarbonylmethyleneoxyphenyl)-6-ethoxycarbonyl-5-(ethoxycarbonylmethyleneaminocarbonylamino)-2,4-pyrimidinediamine. LCMS: ret. time: 25.76 min.; purity: 96%; MS (m/e): 683 (MH⁺).

7.3.690 N2,N4-Bis(4-ethoxycarbonylmethyleneoxyphenyl)-6-ethoxycarbonyl-5-(cyclopentylaminocarbonylamino)-2,4-pyrimidinediamine (R926588)

In like manner to the preparation of N2,N4-bis(4-ethoxycarbonylmethyleneoxyphenyl)-6-ethoxycarbonyl-5-(phenylaminocarbonylamino)-2,4-pyrimidinediamine, the reaction of 5-amino-N2,N4-bis(4-ethoxycarbonylmethyleneoxyphenyl)-6-ethoxycarbonyl-2,4-pyrimidinediamine with cyclopentyl isocyanate gave N2,N4-bis(4-ethoxycarbonylmethyleneoxyphenyl)-6-ethoxycarbonyl-5-(cyclopentylaminoacrbonylamino)-2,4-pyrimidinediamine . LCMS: ret. time: 27.36 min.; purity: 83%; MS (m/e): 665 (MH⁺).

7.3.691 N2,N4-Bis(4-ethoxycarbonylmethyleneoxyphenyl)-6-ethoxycarbonyl-5-(chloroacetylaminocarbonylamino)-2,4-pyrimidinediamine (R926589)

In like manner to the preparation of N2,N4-bis(ethoxycarbonylmethyleneoxyphenyl)-6-ethoxycarbonyl-5-(N-phenylformyl-amino)-2,4-pyrimidinediamine, the reaction of N5-amino-N2,N4-bis(ethoxycarbonylmethyleneoxyphenyl)-6-ethoxycarbonyl-2,4-pyrimidinediamine with chloroacetylformyl isocyanate gave N2,N4-bis(4-ethoxycarbonylmethyleneoxyphenyl)-6-ethoxycarbonyl-5-(chloroacetylaminocarbonylamino)-2,4-pyrimidinediamine. LCMS: ret. time: 26.60 min.; purity: 100%; MS (m/e): 580 (MH⁺).

7.3.692 (R920669): N2,N4-Bis(3,4-ethylenedioxyphenyl)-5-trifluoro-2,4-pyridinediamine

A mixture of 2,4-dichloro-5-trifluoromethylpyrimidine (416 mg, 1.9 mmol), 3,4-ethylenedioxyaniline (0.5 mL, 4.1 mmol), and concentrated HCl (0.1 mL) in 1:9 acetone/H₂O (10 mL) was heated to reflux. After 1 h, the reaction was complete as determined by TLC. The mixture was cooled to room temperature and EtOAc (30 mL) was added. The organic layer was washed with 2 N HCl (2 x 15 mL), water (15 mL), and dried (Na₂SO₄). The organic layer was filtered through a silica gel pad, washing the filter cake with EtOAc, and concentrated. The material was purified by chromatography (silica gel, 95:5 dichloromethane/ethyl acetate) to afford N2,N4-bis(3,4-ethylenedioxyphenyl)-5-trifluoro-2,4-pyridinediamine (380 mg, 44%): *R_f* 0.27 (silica gel, 9.5:0.5 dichloromethane/ethyl acetate); mp 141-143 °C; ¹H NMR (300 MHz, CDCl₃) δ 8.25 (s, 1H), 7.07 (m, 2H), 6.99 (bs, 1H), 6.93-6.84 (m, 3H), 6.77-6.74 (m, 1H), 6.67 (bs, 1H), 4.29-4.24 (m, 8H); ¹³C NMR (75 MHz, CDCl₃) δ 161.2, 157.9, 155.8, 143.7, 132.6, 131.1, 117.5, 117.3, 114.4, 113.2, 110.3, 64.7, 64.5; IR (ATR) 3446 cm⁻¹; ESI MS *m/z* 447 [C₂₁H₁₇F₃N₄O₄ + H]⁺; HPLC (Method C) >99% (AUC), *t_R* = 8.5 min. Anal. Calcd for C₂₁H₁₇F₃N₄O₄: C, 56.50; H, 3.84; N, 12.55. Found: C, 56.46; H, 4.41; N, 12.57.

7.3.693 (R920668): N4-(3,4-Ethylenedioxyphenyl)-5-fluoro-N2-(3-pyridyl)-2,4-pyrimidinediamine

A mixture of 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine (280 mg, 1 mmol), 3-aminopyridine (113 mg, 1.2 mmol), sodium *t*-butoxide (134 mg, 1.4 mmol), binap (38 mg, 0.06 mmol), and palladium(II)acetate (14 mg, 0.06 mmol) in 9 mL of toluene was purged with N₂ (3 cycles of alternating N₂ and vacuum). The mixture was heated to 80 °C (oil-bath temperature). After 24 h, the mixture was cooled to room temperature and EtOAc (30 mL) and of water (10 mL) was added. After stirring 15 min, the precipitate was collected by filtration. A ¹H NMR spectrum and ESI mass spectrum of the solid (150 mg) indicated the product (TLC analysis of the organic layer of the filtrate detected only starting materials). The crude product was slurried in 2 N HCl and the mixture was filtered. The filtrate was neutralized with 10% aqueous NaOH and concentrated. The material was slurried with MeOH and the solids removed by filtration. The concentrated material was slurried in CH₃CN and TFA was added to afford a solution. *N,N*-diisopropylethylamine was added to the solution and the solid was collected by filtration, washing with CH₃CN followed by Et₂O to afford N4-(3,4-ethylenedioxyphenyl)-

5-fluoro-N2-(3-pyridyl)-2,4-pyrimidinediamine (55 mg, 14%): R_f 0.42 (silica gel, 4:1:0.1:0.1 dichloromethane/ethyl acetate/methanol/concentrated ammonium hydroxide); mp 251-253 °C; ^1H NMR (300 MHz, DMSO- d_6) δ 9.38 (s, 1H), 9.26 (s, 1H), 8.74 (s, 1H), 8.20-8.17 (m, 1H), 8.09-8.08 (m, 2H), 7.29-7.28 (m, 1H), 7.23-7.17 (m, 2H), 6.83-6.80 (m, 1H), 4.24 (m, 4H); ^{13}C NMR (75 MHz, DMSO- d_6) δ 155.2, 149.8, 142.9, 141.6, 140.5, 140.0, 139.8, 139.7, 137.5, 132.1, 124.8, 123.0, 116.4, 115.1, 110.9, 64.1, 64.0; IR (ATR) 3264, 3195 cm^{-1} ; APCI MS m/z 340 [$\text{C}_{17}\text{H}_{14}\text{FN}_5\text{O}_2 + \text{H}$] $^+$. Anal. Calcd for $\text{C}_{17}\text{H}_{14}\text{FN}_5\text{O}_2 \cdot 0.5\text{H}_2\text{O}$: C, 58.70; H, 4.20; N, 20.13. Found: C, 58.71; H, 4.20; N, 19.51.

7.3.694 (R920664): N4-(3,4-Ethylenedioxyphenyl)-5-fluoro-N2-(4-n-hexyloxyphenyl)-2,4-pyrimidindiamine

To a magnetically stirred solution of 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine (0.25 g, 0.89 mmol) in ethylene glycol (3.0 mL) under nitrogen at room temperature was added *N,N*-diisopropylethylamine (0.12 g, 0.89 mmol) followed by 4-hexyloxyaniline (0.27 g, 1.4 mmol). The reaction mixture was heated to 170 °C for 5.5 h, cooled to room temperature and partitioned between water (20 mL) and chloroform (20 mL). The aqueous layer was extracted with chloroform (20 mL) and the combined organic layers were dried (Na_2SO_4), filtered and concentrated in vacuo. The crude brown solid was purified by chromatography (silica gel, 2:1 hexanes/ethyl acetate) to afford N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(4-n-hexyloxyphenyl)-2,4-pyrimidindiamine (0.09 g, 23%) as a white solid: R_f 0.53 (silica gel, 4:1 chloroform/ethyl acetate); mp 115-117 °C; ^1H NMR (500 MHz, CDCl_3) δ 7.90 (d, J = 3.2 Hz, 1H), 7.40 (d, J = 8.9 Hz, 2H), 7.29 (d, J = 2.5 Hz, 2H), 6.98 (d, J = 8.8 Hz, 1H), 6.88-6.82 (m, 3H), 6.61 (s, 1H), 4.29 (d, J = 3.1 Hz, 4H), 3.94 (t, J = 6.6, 6.7 Hz, 2H), 1.77 (m, 2H), 1.47 (m, 2H), 1.35 (m, 4H), 0.92 (m, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 156.3, 155.1, 150.3, 143.6, 142.7, 140.3, 140.07, 139.4, 133.0, 131.7, 121.9, 117.3, 115.0, 114.7, 110.8, 68.6, 64.6, 31.8, 29.5, 25.9, 22.8, 14.2; IR (ATR) 3357 cm^{-1} ; ESI MS m/z 439 [$\text{C}_{24}\text{H}_{27}\text{FN}_4\text{O}_3 + \text{H}$] $^+$; HPLC (Method B) 98.5% (AUC), t_R = 7.9 min. Anal. Calcd for $\text{C}_{24}\text{H}_{27}\text{FN}_4\text{O}_3$: C, 65.74; H, 6.21; N, 12.78. Found: C, 65.34; H, 6.19; N, 12.96.

7.3.695 (R920666): N2-(4-n-Butyloxyphenyl)-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine

To a magnetically stirred solution of 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine (0.25 g, 0.89 mmol) in ethylene glycol (3.0 mL) under nitrogen at

room temperature was added *N,N*-diisopropylethylamine (0.12 g, 0.89 mmol) followed by 4-butoxyaniline (0.18 g, 1.1 mmol). The reaction mixture was heated to 185 °C for 5 h, cooled to room temperature, and partitioned between water (20 mL) and ethyl acetate (20 mL). The aqueous layer was extracted with ethyl acetate (20 mL) and the combined organic layers were dried (Na₂SO₄), filtered and concentrated in vacuo. The crude brown solid was purified by chromatography (silica gel, 2:1 hexanes/ethyl acetate) to afford N2-(4-n-Butyloxyphenyl)-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyridinediamine (0.18 g, 49%) as a tan solid: *R_f* 0.66 (silica gel, 4:1 chloroform/ethyl acetate); mp 133-135 °C; ¹H NMR (300 MHz, CDCl₃) δ 7.89 (d, *J* = 3.2 Hz, 1H), 7.39 (d, *J* = 8.9 Hz, 2H), 7.28 (d, *J* = 2.5 Hz, 1H), 6.95 (dd, *J* = 8.7, 2.5 Hz, 1H) 6.90-6.81 (m, 4H), 6.60 (d, *J* = 2.4 Hz, 1H), 4.27 (s, 4H), 3.94 (t, *J* = 6.5 Hz, 2H), 1.80-1.71 (m, 2H), 1.55-1.42 (m, 2H), 0.97 (t, *J* = 7.3 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 156.3, 155.1, 150.4, 143.6, 142.7, 140.3, 140.0, 139.4, 133.0, 131.7, 121.9, 117.3, 115.0, 114.7, 110.8, 68.2, 64.7, 64.5, 31.6, 19.4, 14.0; IR (ATR) 3356 cm⁻¹; ESI MS *m/z* 411 [C₂₂H₂₃FN₄O₃ + H]⁺; HPLC (Method A) >99% (AUC), *t_R* = 17.3 min. Anal. Calcd for C₂₂H₂₃FN₄O₃: C, 64.38; H, 5.65; N, 13.65. Found: C, 62.64; H, 5.59; N, 13.15.

7.3.696 (R920670): N4-(4-ethyloxyphenyl)-N2-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine

To a solution of 2-chloro-N4-(4-ethyloxyphenyl)-5-fluoro-4-pyrimidineamine (0.25 g, 0.93 mmol) in ethylene glycol (3 mL) under nitrogen at room temperature was added *i*-Pr₂EtN, 0.93 mmol) followed by 3,4-ethylenedioxyaniline (0.17 g, 1.12 mmol). The reaction mixture was heated to 200 °C for 5 h and then cooled to room temperature. The mixture was partitioned between H₂O (20 mL) and EtOAc (20 mL) and the aqueous layer was extracted with EtOAc (20 mL). The combined organic layers were dried (Na₂SO₄), filtered, and concentrated in vacuo. The crude brown solid was purified by chromatography (2:1 CHCl₃/EtOAc) to afford N4-(4-ethyloxyphenyl)-N2-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine (0.21 g, 60%) as a tan solid: *R_f* 0.42 (4:1 CHCl₃/EtOAc); mp 163.8-167.2 °C (DSC); ¹H NMR (300 MHz, CDCl₃) δ 7.89 (d, *J* = 2.8 Hz, 1H), 7.50-7.45 (m, 2H), 7.17 (d, *J* = 2.5 Hz, 1H), 6.92-6.86 (m, 3H), 6.80-6.75 (m, 2H), 6.64 (bs, 1H), 4.26-4.21 (m, 4H), 4.03 (q, *J* = 7.0, 2H), 1.42 (t, *J* = 6.9 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 156.1, 150.6, 143.6, 142.8, 140.3, 140.0, 139.5, 139.3, 134.0, 130.8, 123.2, 117.2, 115.1, 113.6, 109.4, 64.6, 64.0, 15.1; IR (ATR) 3403 cm⁻¹; ESI MS *m/z* 383 [C₂₀H₁₉FN₄O₃

+ H]⁺; HPLC (Method A) 98.1% (AUC), *t*_R = 12.0 min. Anal. Calcd for C₂₀H₁₉FN₄O₃: C, 62.82; H, 5.01; N, 14.65. Found: C, 62.06; H, 5.01; N, 14.35.

7.3.697 (R920671): N4-(4-n-Butyloxyphenyl)-N2-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyridinediamine

5 In like manner to the preparation of N4-(4-ethyloxyphenyl)-N2-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine, the reaction of 2-chloro-N4-(4-n-butyloxyphenyl)-5-fluoro-4-pyrimidineamine with 3,4-ethylenedioxyaniline gave N4-(4-n-butyloxyphenyl)-N2-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyridinediamine. The crude product was purified by chromatography (2:1 CHCl₃/EtOAc) ; (0.17 g, 52%) as a tan solid:
 10 *R*_f 0.51 (4:1 CHCl₃/EtOAc); mp 149.6-151.4 °C (DSC); ¹H NMR (300 MHz, CDCl₃) δ 7.88 (d, *J* = 3.4 Hz, 1H), 7.47 (d, *J* = 8.8 Hz, 2H), 7.18 (d, *J* = 2.4 Hz, 1H), 6.91-6.86 (m, 3H), 6.78-6.75 (m, 2H), 6.62 (bs, 1H), 4.26-4.22 (m, 4H), 3.96 (t, *J* = 6.5, 2H), 1.82-1.73 (m, 2H), 1.56-1.44 (m, 2H), 0.98 (t, *J* = 7.4 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 156.1, 150.8, 143.6, 142.8, 140.2, 139.9, 139.5, 139.2, 133.9, 130.7, 123.1, 117.1, 115.0, 113.5, 109.4,
 15 68.2, 64.6, 31.6, 19.4, 14.0; IR (ATR) 3365 cm⁻¹; ESI MS *m/z* 411 [C₂₂H₂₃FN₄O₃ + H]⁺; HPLC (Method A) 99.0% (AUC), *t*_R = 13.2 min. Anal. Calcd for C₂₂H₂₃FN₄O₃: C, 64.38; H, 5.65; N, 13.65. Found: C, 63.63; H, 5.60; N, 13.38.

7.3.698 (R920672): N4-(4-n-Hexyloxyphenyl)-N2-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyridinediamine

20 In like manner to the preparation of N4-(4-ethyloxyphenyl)-N2-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine, the reaction of 2-chloro-N4-(4-n-hexyloxyphenyl)-5-fluoro-4-pyrimidineamine with 3,4-ethylenedioxyaniline gave N4-(4-n-hexyloxyphenyl)-N2-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyridinediamine. The crude product was purified by chromatography (2:1 CHCl₃/EtOAc) (0.22 g, 69%) as a tan solid: *R*_f
 25 0.54 (4:1 CHCl₃/EtOAc); mp 124.0-125.2 °C (DSC); ¹H NMR (300 MHz, CDCl₃) δ 7.88 (d, *J* = 3.2 Hz, 1H), 7.47 (d, *J* = 8.9 Hz, 2H), 7.18 (d, *J* = 2.4 Hz, 1H), 6.91-6.86 (m, 3H), 6.78-6.74 (m, 2H), 6.62 (d, *J* = 1.8 Hz, 1H), 4.26-4.22 (m, 4H), 3.96 (t, *J* = 6.5, 2H), 1.83-1.74 (m, 2H), 1.51-1.42 (m, 2H), 1.36-1.32 (m, 4H), 0.93-0.89 (t, *J* = 6.7 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 156.1, 150.5, 143.5, 143.0, 142.8, 140.2, 139.9, 139.5, 139.2, 133.9,
 30 130.7, 123.1, 117.1, 115.0, 113.5, 109.3, 68.5, 64.7, 64.5, 31.8, 29.5, 25.9, 22.8, 14.2; IR (ATR) 3378 cm⁻¹; ESI MS *m/z* 439 [C₂₄H₂₇FN₄O₃ + H]⁺; HPLC (Method A) >99% (AUC),

$t_R = 14.6$ min. Anal. Calcd for $C_{24}H_{27}FN_4O_3$: C, 65.74; H, 6.21; N, 12.78. Found: C, 65.52; H, 6.23; N, 12.66.

7.3.699 (R920818): 5-Fluoro-N4-(3-hydroxyphenyl)-N2-[4-(1,2,3,4-tetrazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine

5 To a mixture of 4-amino-[(1,2,3,4-tetrazol-5-yl)methyleneoxy]benzene (1.2 g, 6.2 mmol), 1-propanol (40 mL) and trifluoroacetic acid (1 mL) was added 2-chloro-5-fluoro-N4-(3-hydroxyphenyl)-4-pyridineamine (1.5 g, 6.2 mmol). The mixture was heated at 110 °C for 17 h and then cooled to room temperature. The purple solid that formed was collected by filtration, washing with 1-propanol (30 mL) to afford 5-Fluoro-N4-(3-hydroxyphenyl)-N2-[4-(1,2,3,4-tetrazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine (1.6 g, 65%) as an off-white solid: R_f 0.55 (6:3:1 $CHCl_3/CH_3OH/NH_4OH$); mp (DSC) 191.2-193.7 °C, 257.2-260.0 °C, 344.7-345.2 °C; 1H NMR (300 MHz, $DMSO-d_6$) δ 9.39 (s, 1H), 9.21 (s, 1H), 9.10 (s, 1H), 8.04 (d, $J = 3.8$ Hz, 1H), 7.59 (d, $J = 9.1$ Hz, 2H), 7.38 (s, 1H), 7.23 (t, $J = 8.1$ Hz, 1H), 7.17 (d, $J = 1.8$ Hz, 1H), 7.05 (t, $J = 8.1$ Hz, 1H), 6.93 (d, $J = 9.1$ Hz, 2H), 6.50 (dd, $J = 1.8, 8.1$ Hz, 1H), 5.40 (s, 2H); ^{13}C NMR (75 MHz, $DMSO-d_6$) δ 157.3, 155.3, 153.5, 151.9, 149.8, 149.7, 141.0 (d, $J_{C-F} = 150.0$ Hz), 139.7, 138.7, 135.0, 128.9, 120.2, 114.8, 110.3, 108.7, 59.6; IR (ATR) 3338, 2923, 2581, 1724, 1661, 1580, 1557 cm^{-1} ; ESI MS m/z 395 [$C_{18}H_{15}FN_8O_2 + H$] $^+$; HPLC (Method A) 96.5% (AUC), $t_R = 6.9$ min.

20 **7.3.700 (R920819): N4-(3-Hydroxyphenyl)-N2-[4-(1H,1,2,3,4-tetrazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine**

To a mixture of 4-amino-[(1H,1,2,3,4-tetrazolyl)methyleneoxy]benzene (0.1 g, 0.5 mmol), 1-propanol (2 mL) and trifluoroacetic acid (0.2 mL) was added 2-chloro-N4-(3-hydroxyphenyl)-4-pyrimidineamine (0.1 g, 0.5 mmol). The mixture was heated at 110 °C for 17 h and then cooled to room temperature. The purple solid that formed was collected by filtration, washing with 1-propanol (5 mL) to afford N4-(3-hydroxyphenyl)-N2-[4-(1H,1,2,3,4-tetrazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine (59.4 mg, 30%) as an off-white solid: R_f 0.51 (6:3:1 $CHCl_3/CH_3OH/NH_4OH$); mp 292-295 °C dec; 1H NMR (300 MHz, $DMSO-d_6$) δ 9.34 (s, 2H), 9.13 (s, 1H), 7.95 (d, $J = 5.8$ Hz, 1H), 7.64 (d, $J = 8.9$ Hz, 2H), 7.39 (s, 1H), 7.19 (t, $J = 8.1$ Hz, 1H), 7.05 (t, $J = 8.1$ Hz, 1H), 6.96 (d, $J = 8.9$ Hz, 2H), 6.43 (dd, $J = 1.4, 8.1$ Hz, 1H), 6.20 (d, $J = 5.8$ Hz, 1H), 5.40 (s, 2H); ^{13}C NMR (75 MHz, $DMSO-d_6$) δ 160.4, 158.5, 157.5, 154.0, 153.7, 152.2, 140.6, 134.4, 129.1, 120.9,

114.7, 111.0, 109.5, 107.2, 98.4, 59.6; IR (ATR) 3321, 2920, 2581, 1649, 1605, 1487 cm^{-1} ; ESI MS m/z 377 [$\text{C}_{18}\text{H}_{16}\text{N}_8\text{O}_2 + \text{H}$] $^+$; HPLC (Method A) 97.6% (AUC), $t_R = 7.6$ min.

7.3.701 (R920820): N4-(3-Hydroxyphenyl)-5-methyl-N2-[4-(1H, 1,2,3,4-tetrazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine

To a mixture of 4-amino-[(1H,1,2,3,4-tetrazolyl)methyleneoxy]benzene (0.2 g, 0.9 mmol), 1-propanol (4 mL) and trifluoroacetic acid (0.2 mL) was added 2-chloro-N4-(3-hydroxyphenyl)-5-methyl-4-pyrimidineamine (0.2 g, 0.9 mmol). The mixture was heated at 110 °C for 17 h and then cooled to room temperature. The purple solid that formed was collected by filtration, washing with 1-propanol (10 mL) to afford N4-(3-hydroxyphenyl)-5-methyl-N2-[4-(1H,1,2,3,4-tetrazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine (0.3 g, 89%) as an off-white solid: R_f 0.44 (6:3:1 $\text{CHCl}_3/\text{CH}_3\text{OH}/\text{NH}_4\text{OH}$); mp (DSC) 255.3-262.4 °C; ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 10.32 (s, 1H), 9.65 (s, 2H), 7.85 (s, 1H), 7.38 (d, $J = 10.5$ Hz, 2H), 7.17 (s, 1H), 7.12 (t, $J = 7.9$ Hz, 1H), 7.06 (s, 1H), 6.90 (d, $J = 10.5$ Hz, 2H), 6.68 (d, $J = 7.9$ Hz, 1H), 5.45 (s, 2H), 2.14 (s, 3H); ^{13}C NMR (75 MHz, $\text{DMSO}-d_6$) δ 161.6, 157.9, 154.5, 153.7, 151.2, 140.4, 138.2, 130.1, 129.4, 123.3, 115.9, 115.4, 113.5, 112.4, 107.5, 59.8, 13.7; IR (ATR) 3214, 3051, 2157, 1632, 1596, 1547 cm^{-1} ; ESI MS m/z 391 [$\text{C}_{19}\text{H}_{18}\text{N}_8\text{O}_2 + \text{H}$] $^+$; HPLC (Method A) >99% (AUC), $t_R = 7.9$ min.

7.3.702 N4-(3-Benzoyloxyphenyl)-N2-[4-(1-methyl-1,2,3,4-tetrazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidineamine [NEED R NO.]

A mixture of N4-(3-benzyloxyphenyl)-2-chloro-4-pyrimidineamine (0.25 g, 0.82 mmol), 4-amino-(1-methyl-1,2,3,4-tetrazol-5-yl)methyleneoxy]-benzene (0.17 g, 0.82 mmol) and trifluoroacetic acid (0.2 mL) in 1-propanol (10 mL) was heated to 110 °C for 24 h. The reaction was concentrated to remove most of the 1-propanol, the crude product was preadsorbed onto silica gel using 95:5 methylene chloride /methanol and purified by flash chromatography (95:5 methylene chloride /methanol) to give N4-(3-benzyloxyphenyl)-N2-[4-(1-methyl-1,2,3,4-tetrazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidineamine as a tan solid (0.20 g, 52%): ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 8.00 (br s, 1H), 7.86 (d, $J = 6.1$ Hz, 1H), 7.53-7.20 (m, 13H), 7.14 (d, $J = 9.0$ Hz, 2H), 6.93 (d, $J = 6.1$ Hz, 1H), 6.13 (d, $J = 6.1$ Hz, 1H), 5.27 (s, 2H), 4.04 (s, 3H); ESI MS m/z 481 [$\text{C}_{26}\text{H}_{24}\text{N}_8\text{O}_2 + \text{H}$] $^+$.

7.3.703 (R920917): N4-(3-hydroxyphenyl)-N2-[4-(1-methyl-1,2,3,4-tetrazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidineamine

A mixture of N4-(3-benzyloxyphenyl)-N2-[4-(1-methyl-1,2,3,4-tetrazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidineamine (0.20 g, 0.42 mmol) and 5% Pd/C (0.10 g) in 14:1 ethanol/concentrated hydrochloric acid (40 mL) was at room temperature was shaken in a hydrogen atmosphere at 50 psi. After 3 h no further hydrogen uptake was observed. The reaction mixture was filtered through diatomaceous earth, the solids washed with 95:5 methylene chloride/methanol and the filtrate concentrated to afford N4-(3-hydroxyphenyl)-N2-[4-(1-methyl-1,2,3,4-tetrazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidineamine (0.16 g, 95%) as a tan solid: R_f 0.23 (95:5 methylene chloride/methanol); mp (DSC) 207.1-212.8, 287.4-295.7 °C; ^1H NMR (300 MHz, DMSO- d_6) δ 10.87 (br s, 1H), 10.81 (br s, 1H), 9.62 (br s, 1H), 8.08-8.06 (m, 1H), 7.72 (d, J = 9.0 Hz, 2H), 7.24 (br s, 1H), 7.20-7.00 (m, 3H), 6.61 (m, 2H), 6.46, (d, J = 6.0 Hz, 1H), 5.38 (s, 2H), 4.40 (s, 3H); ^{13}C NMR (75 MHz, DMSO- d_6) δ 161.3, 160.1, 157.0, 154.3, 151.6, 141.7, 137.6, 129.1, 128.6, 123.4, 114.4, 111.9, 111.5, 108.3, 98.6, 59.6, 38.0; IR (ATR) 2975, 1639, 1602, 1521 cm^{-1} ; ESI MS m/z 391 [$\text{C}_{19}\text{H}_{18}\text{N}_8\text{O}_2 + \text{H}$] $^+$; HPLC (Method A) 94.9 % (AUC), t_R = 8.19 min.

7.3.704 N4-(3-Benzyloxyphenyl)-N2-[4-(2-methyl-1,2,3,4-tetrazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidineamine [NEED R NO.]

A mixture of N4-(3-benzyloxyphenyl)-2-chloro-4-pyrimidineamine (0.52 g, 1.69 mmol), 4-amino-(2-methyl-1,2,3,4-tetrazol-5-yl)methyleneoxy]benzene (0.34 g, 1.69 mmol) and trifluoroacetic acid (0.4 mL) in 1-propanol (10 mL) was heated to 110 °C for 24 h. The reaction was concentrated to remove most of the 1-propanol. The crude product was preadsorbed onto silica gel using 95:5 methylene chloride /methanol and purified by flash chromatography (95:5 methylene chloride /methanol) affording the requisite product N4-(3-benzyloxyphenyl)-N2-[4-(2-methyl-1,2,3,4-tetrazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidineamine as a tan solid (0.41 g, 51%): ^1H NMR (300 MHz, DMSO- d_6) δ 7.85 (d, J = 6.1 Hz, 1H), 7.49-7.04 (m, 14H), 6.93 (d, J = 9.0 Hz, 2H), 6.60-6.72 (m, 1H), 6.11 (d, J = 6.1 Hz, 1H), 5.14 (s, 2H), 4.34 (s, 3H); ESI MS m/z 481 [$\text{C}_{26}\text{H}_{24}\text{N}_8\text{O}_2 + \text{H}$] $^+$

7.3.705 (R920910): N4-(3-Hydroxyphenyl)-N2-[4-(2-methyl-1,2,3,4-tetrazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidineamine

A mixture of N4-(3-benzyloxyphenyl)-N2-[4-(2-methyl-1,2,3,4-tetrazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidineamine (0.40 g, 0.42 mmol) and 5% Pd/C (0.10 g) in 14:1 ethanol/concentrated hydrochloric acid (40 mL) at room temperature was shaken in an

atmosphere of hydrogen at 50 psi. After 3 h no further hydrogen uptake was observed. The reaction mixture was filtered through diatomaceous earth, the solids washed with 95:5 methylene chloride/methanol and the filtrate concentrated to afford N4-(3-hydroxyphenyl)-N2-[4-(2-methyl-1,2,3,4-tetrazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidineamine (0.29 mg, 89%) as a beige solid: R_f 0.43 (95:5 methylene chloride/methanol); mp 140-152 °C; ^1H NMR (300 MHz, DMSO- d_6) δ 10.24 (br s, 1H), 9.98 (br s, 1H), 9.52 (br s, 1H), 7.94 (d, J = 6.6 Hz, 2H), 7.54 (d, J = 8.8 Hz, 2H), 7.43 (s, 1H), 7.26 (s, 1H), 7.18-7.01 (m, 3H), 6.53, (d, J = 7.5 Hz, 1H), 6.37, (d, J = 6.6 Hz, 1H), 5.52 (s, 2H), 4.13 (s, 3H); ^{13}C NMR (75 MHz, DMSO- d_6) δ 160.2, 157.2, 154.5, 153.0, 151.2, 146.8, 139.9, 131.8, 128.7, 122.3, 114.7, 111.4, 110.5, 107.5, 99.5, 59.5, 33.3; IR (ATR) 3042, 1578, 1504, 1459 cm^{-1} ; ESI MS m/z 391 [$\text{C}_{19}\text{H}_{18}\text{N}_8\text{O}_2 + \text{H}$] $^+$; HPLC (Method A) 95.8 % (AUC), t_R = 8.82 min.

7.3.706 (R920861): 5-Fluoro-N4-(3-hydroxyphenyl)-N2-[4-(1-methyl-1,2,3,4-tetrazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidineamine

A mixture of 2-chloro-5-fluoro-N4-(3-hydroxyphenyl)-4-pyrimidineamine (0.22 g, 0.93 mmol, 4-amino-[(1-methyl-1,2,3,4-tetrazol-5-yl)methyleneoxy]-benzene (0.19 g, 0.93 mmol) and trifluoroacetic acid (0.2 mL) in 1-propanol (8 mL) was heated to 110 °C for 24 h. The reaction was concentrated to remove most of the 1-propanol. The crude product was preadsorbed onto silica gel using 95:5 methylene chloride/methanol and purified by flash chromatography (95:5 methylene chloride /methanol) affording the requisite product 5-fluoro-N4-(3-hydroxyphenyl)-N2-[4-(1-methyl-1,2,3,4-tetrazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidineamine as a purple solid (0.18 g, 49%): R_f 0.47 (95:5 methylene chloride/methanol); mp 219-224 °C; ^1H NMR (300 MHz, DMSO- d_6) δ 9.36 (s, 1H), 9.18 (s, 1H), 9.06 (s, 1H), 8.05 (d, J = 6.0 Hz, 1H), 7.60 (d, J = 9.0 Hz, 2H), 7.27 (d, J = 9.0 Hz, 1H), 7.09 (t, J = 8.0 Hz, 2H), 6.94 (d, J = 9.0 Hz, 2H), 6.49 (dd, J = 8.0, 2.1 Hz, 1H), 5.45 (s, 2H), 4.11 (s, 3H); ^{13}C NMR (75 MHz, DMSO- d_6) δ 157.4, 155.5, 151.7, 151.6, 149.6, 149.5, 142.0, 142.0, 139.3 (d, $J_{\text{C-F}}$ = 127.5 Hz), 135.3, 128.9, 120.1, 114.9, 112.3, 110.3, 108.5, 58.5, 33.9; IR (ATR) 3278, 1586, 1542, 1508 cm^{-1} ; ESI MS m/z 409 [$\text{C}_{19}\text{H}_{17}\text{FN}_8\text{O}_2 + \text{H}$] $^+$; HPLC (Method A) 98.2 % (AUC), t_R = 7.69 min. Anal. Calcd for $\text{C}_{19}\text{H}_{17}\text{FN}_8\text{O}_2 \cdot 0.5 \text{H}_2\text{O}$: C, 54.74; H, 4.23; N, 26.88. Found: C, 54.55; H, 4.02; N, 26.62.

7.3.707 (R920860): 5-Fluoro-N4-(3-hydroxyphenyl)-N2-[4-(1-methyl-1,2,3,4-tetrazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidineamine

A mixture of 2-chloro-5-fluoro-N4-(3-hydroxyphenyl)-4-pyrimidineamine (0.31 g, 1.28 mmol), 4-amino-[(2-methyl-1,2,3,4-tetrazol-5-yl)methyleneoxy]-benzene (0.26 g, 1.28 mmol) and trifluoroacetic acid (0.2 mL) in 1-propanol (8 mL) was heated at 110 °C for 24 h. The reaction was concentrated to remove most of the 1-propanol. The crude product was preadsorbed onto silica gel using 95:5 methylene chloride/methanol and purified by flash chromatography (95:5 methylene chloride /methanol) to give 5-fluoro-N4-(3-hydroxyphenyl)-N2-[4-(2-methyl-1,2,3,4-tetrazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidineamine as a purple solid (0.20 g, 37 %): R_f 0.63 (95:5 methylene chloride/methanol); mp 220-224 °C; ^1H NMR (300 MHz, DMSO- d_6) δ 9.36 (s, 1H), 9.17 (s, 1H), 9.02 (s, 1H), 8.05 (d, J = 2.8 Hz, 1H), 7.57 (d, J = 9.1 Hz, 2H), 7.27 (d, J = 8.0 Hz, 1H), 7.10 (dt, J = 2.8, 8.0 Hz, 2H), 6.91 (d, J = 9.1 Hz, 2H), 6.49 (dd, J = 8.0, 2.8 Hz, 1H), 5.29 (s, 2H), 4.39 (s, 3H); ^{13}C NMR (75 MHz, DMSO- d_6) δ 162.2, 157.4, 155.5, 152.1, 149.6, 149.5, 140.9 (d, J_{C-F} = 142.0 Hz), 140.5, 140.2, 138.7, 134.8, 128.9, 120.2, 114.5, 112.2, 110.2, 108.5, 60.5, 38.5; IR (ATR) 3274, 1587, 1507 cm^{-1} ; ESI MS m/z 409 $[\text{C}_{19}\text{H}_{17}\text{FN}_8\text{O}_2 + \text{H}]^+$; HPLC (Method A) 97.2 % (AUC), t_R = 8.04 min. Anal. Calcd for $\text{C}_{19}\text{H}_{17}\text{FN}_8\text{O}_2$: C, 55.88; H, 4.20; N, 27.44. Found: C, 55.56; H, 4.10; N, 27.17.

7.3.708 (R920894): N4-(3-Hydroxyphenyl)-5-methyl-N2-[4-(1-methyl-1,2,3,4-tetrazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidineamine

A mixture of 2-chloro-N4-(3-hydroxyphenyl)-5-methyl-4-pyrimidineamine (0.20 g, 0.85 mmol), 4-amino-(1-methyl-1,2,3,4-tetrazol-5-yl)methyleneoxy]-benzene (0.17 g, 0.85 mmol) and trifluoroacetic acid (0.2 mL) in 1-propanol (8 mL) was heated at 110 °C for 24 h. The reaction was concentrated to remove most of the 1-propanol. The crude product was preadsorbed onto silica gel using 95:5 methylene chloride/methanol and purified by flash chromatography (95:5 methylene chloride /methanol) to give N4-(3-hydroxyphenyl)-5-methyl-N2-[4-(1-methyl-1,2,3,4-tetrazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidineamine as a purple solid (0.18 g, 52%): R_f 0.61 (95:5 methylene chloride/methanol); mp 209-211 °C; ^1H NMR (300 MHz, DMSO- d_6) δ 9.30 (s, 1H), 8.82 (s, 1H), 8.13 (s, 1H), 7.83 (s, 1H), 7.60 (d, J = 9.0 Hz, 2H), 7.18-7.05 (m, 3H), 6.89 (d, J = 9.0 Hz, 2H), 6.48 (t, J = 7.1 Hz, 1H), 5.27 (s, 2H), 4.39 (s, 3H), 2.08 (s, 3H); ^{13}C NMR (75 MHz, DMSO- d_6) δ 161.7, 158.6, 157.5, 156.7, 154.7, 151.2, 140.2, 134.6, 134.6, 128.1, 119.3, 114.0, 112.6, 109.4, 108.9,

104.7, 59.8, 38.0, 12.9; IR (ATR) 3003, 1602, 1581, 1531, 1507 cm^{-1} ; ESI MS m/z 405 $[\text{C}_{20}\text{H}_{20}\text{N}_8\text{O}_2 + \text{H}]^+$; HPLC (Method A) 96.8 % (AUC), t_R = 8.23 min.

7.3.709 (R920893): N4-(3-Hydroxyphenyl)-5-methyl-N2-[4-(2-methyl-1,2,3,4-tetrazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidineamine

A mixture of 2-chloro-N4-(3-hydroxyphenyl)-5-methyl-4-pyrimidineamine (0.20 g, 0.85 mmol), 4-amino-(2-methyl-1,2,3,4-tetrazol-5-yl)methyleneoxy-benzene (0.17 g, 0.85 mmol) and trifluoroacetic acid (0.2 mL) in 1-propanol (8 mL) was heated at 110 °C for 24 h. The reaction was concentrated to remove most of the 1-propanol. The crude product was preadsorbed onto silica gel using 95:5 methylene chloride/methanol and purified by flash chromatography (95:5 methylene chloride /methanol) to give N4-(3-Hydroxyphenyl)-5-methyl-N2-[4-(2-methyl-1,2,3,4-tetrazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidineamine as a purple solid (0.14 g, 42%): R_f 0.44 (95:5 methylene chloride/methanol); mp 219-221 °C; ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 9.32 (s, 1H), 8.85 (s, 1H), 8.13 (s, 1H), 7.85 (s, 1H), 7.64 (d, J = 9.0 Hz, 2H), 7.20-7.07 (m, 3H), 6.91 (d, J = 9.0 Hz, 2H), 6.50 (dd, J = 8.0, 1.2 Hz, 1H), 5.45 (s, 2H), 4.12 (s, 3H), 2.09 (s, 3H); ^{13}C NMR (75 MHz, $\text{DMSO}-d_6$) δ 158.0, 157.0, 156.1, 154.3, 150.6, 150.0, 139.6, 134.6, 127.5, 118.6, 113.7, 112.0, 108.8, 108.2, 104.2, 57.4, 32.7, 12.3; IR (ATR) 3428, 1595, 1567, 1509 cm^{-1} ; ESI MS m/z 405 $[\text{C}_{20}\text{H}_{20}\text{N}_8\text{O}_2 + \text{H}]^+$; HPLC (Method A) 98.5 % (AUC), t_R = 7.89 min. Anal. Calcd for $\text{C}_{20}\text{H}_{20}\text{N}_8\text{O}_2 \cdot \text{H}_2\text{O}$: C, 57.00; H, 5.02; N, 26.59. Found: C, 56.86; H, 4.92; N, 26.50.

7.3.710 N2,N4-Bis(4-ethoxycarbonylmethyleneoxyphenyl)-5-(1,2,3,4-tetrazol-5-yl)-2,4-pyrimidinediamine (R925810)

In a manner similar to experiment #, N2,N4-bis(4-ethoxycarbonylmethyleneoxyphenyl)-5-cyano-2,4-pyrimidinediamine and sodium azide were reacted to yield N2,N4-bis(4-ethoxycarbonylmethyleneoxyphenyl)-5-(1,2,3,4-tetrazol-5-yl)-2,4-pyrimidinediamine. LCMS: ret. time: 25.8 min.; purity: 95%; MS: 535 (MH^+).

7.3.711 N2-[4-(N-Cyclopropylmethylamino)carbonylmethyleneoxyphenyl]-5-ethoxycarbonyl-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine (R925838)

In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, the reaction of 5-ethoxycarbonyl-N4-(3-hydroxyphenyl)-N2-(methoxycarbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine with cyclopropylmethylamine gave N2-[4-(N-

cyclopropylmethylamino)carbonylmethyleneoxyphenyl]-5-ethoxycarbonyl-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine. LCMS: MS (m/e): 478 (MH⁺).

7.3.712 5-Ethoxycarbonyl-N4-(3-hydroxyphenyl)-N2-[4-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R925839)

In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, the reaction of 5-ethoxycarbonyl-N4-(3-hydroxyphenyl)-N2-(methoxycarbonylmethyleneoxyphenyl)-2,4-pyridinediamine with methylamine hydrochloride gave 5-ethoxycarbonyl-N4-(3-hydroxyphenyl)-N2-[4-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. LCMS: MS (m/e): 438 (MH⁺).

7.3.713 N2-[4-(N-2,3-Dihydroxypropylamino)carbonylmethyleneoxyphenyl]-5-ethoxycarbonyl-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine (R925840)

In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, the reaction of 5-ethoxycarbonyl-N4-(3-hydroxyphenyl)-N2-(methoxycarbonylmethyleneoxyphenyl)-2,4-pyridinediamine with 3-amino-1,2-propanediol gave N2-[4-(N-2,3-dihydroxypropylamino)carbonylmethyleneoxyphenyl]-5-ethoxycarbonyl-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine. LCMS: MS (m/e): 498 (MH⁺).

7.3.714 N2,N4-Bis[4-[N-(3-methoxybenzylamino)carbonylmethyleneoxy]phenyl]-5-bromo-2,4-pyrimidinediamine (R925841)

In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, the reaction of N2,N4-bis[4-ethoxycarbonylmethyleneoxyphenyl]-5-bromo-2,4-pyrimidinediamine with 3-methoxybenzylamine gave N2,N4-bis[4-[N-(3-methoxybenzylamino)carbonylmethyleneoxy]phenyl]-5-bromo-2,4-pyrimidinediamine. LCMS: ret. time: 25.94 min.; purity: 95 %; MS (m/e): 727 (MH⁺).

7.3.715 5-Bromo-N4-[4-[(N-cyclopropylmethylamino)carbonylmethyleneoxyphenyl]-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine (R925842)

In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, the reaction of 5-bromo-N4-(4-ethoxycarbonylmethyleneoxyphenyl)-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine with cyclopropylmethylamine gave 5-bromo-N4-[4-(N-cyclopropylmethylamino)carbonylmethyleneoxyphenyl]-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine. LCMS: ret. time: 20.63 min.; purity: 100 %; MS (m/e): 485 (MH⁺).

7.3.716 5-Bromo-N2-(3-hydroxyphenyl)-N4-[4-(N-3-methoxybenzylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R925843)

In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, the reaction of 5-bromo-N4-(4-ethoxycarbonylmethyleneoxyphenyl)-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine with 3-methoxybenzylamine gave 5-bromo-N2-(3-hydroxyphenyl)-N4-[4-(N-3-methoxybenzylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. LCMS: ret. time: 22.34 min.; purity: 90 %; MS (m/e): 551 (MH⁺).

7.3.717 N4-(3,4-Ethylenedioxyphenyl)-5-fluoro-N2-(2-carboxybenzofuran-5-yl)-2,4-pyrimidinediamine (R926698)

In a manner similar to the preparation of N4-(4-*tert*-butylphenyl)-5-fluoro-N2-(2,3-dihydro-2-carboxybenzofuran-5-yl)-2,4-pyrimidinediamine, N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(2-methoxycarbonylbenzofuran-5-yl)-2,4-pyrimidinediamine and LiOH were reacted to yield N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(2-carboxybenzofuran-5-yl)-2,4-pyrimidinediamine.

7.3.718 N2,N4-Bis(4-trifluoromethylphenyl)-5-fluoro-2,4-pyrimidinediamine (R926016)

In a manner similar to the preparation of N2-N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidineamine, the reaction of 2,4-dichloro-5-fluoropyrimidine with 4-trifluoromethylaniline gave N2,N4-bis(4-trifluoromethylphenyl)-5-fluoro-2,4-pyrimidinediamine. ¹H NMR (CDCl₃): δ 8.06 (bs, 1H), 7.75 (d, 2H, J= 9 Hz), 7.67 (d, 2H, J= 9Hz), 7.63 (d, 2H, J= 9Hz), 7.54 (d, 2H, J= 9 Hz), 7.19 (bs, 1H), 6.96 (s, 1H); ¹⁹F NMR (CDCl₃): δ -17598 (s, 3F), -17676 (s, 3F), -46549 (s, 1F); HPLC: 85% pure.

7.3.719 N2-(3,4-Ethylenedioxyphenyl)-N4-(3,4-methylenedioxyphenylhydrazinyl)-5-fluoro-2-pyrimidineamine (R926406)

In a manner similar to the preparation of N2-(3-hydroxyphenyl)-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidineamine, the reaction of 2-chloro-5-fluoro N4-(3,4-methylenedioxyphenylhydrazinyl)-4-pyrimidineamine with 3,4-ethylenedioxyaniline gave N2-(3,4-ethylenedioxyphenyl)-5-fluoro-N4-(3,4-methylenedioxyphenylhydrazinyl)-2-pyrimidineamine. ¹H NMR (CD₃OD): δ 7.82 (d, 1H, J= 3.6 Hz), 7.52 (dd, 1H, J= 1.8 and 7.5 Hz), 7.40 (d, 1H, J= 1.2 Hz), 7.14 (d, 1H, J= 2.4 Hz), 6.92 (d, 1H, J= 8.4 Hz), 6.85 (dd, 1H, J= 2.1 and 8.7 Hz), 6.45 (d, 1H, J= 9Hz), 6.06 (s, 2H), 4.10 (s, 4H); LCMS: ret. time: 12.14 min.; purity: 88%; MS (m/e): 426 (MH⁺).

7.3.720 N2,N4-Bis(4-ethoxycarbonylmethylenedioxyphenyl)-6-ethoxycarbonyl-5-nitro-2,4-pyrimidinediamine (R926566)

To a solution of 2,4-dichloro-5-nitropyrimidine (0.264 g, 1 mmol) in EtOAc (10 mL) at 0 °C was added diisopropylethyl amine (0.200 mL) followed by ethyl 4-aminophenoxy acetate (0.585 g, 3 mmol) and then shaken at room temperature for 2h. The reaction was quenched with water and extracted with EtOAc. The EtOAc extract was washed with 2N HCl and water. The solvent was evaporated and the residue was purified by crystallization using EtOAc/hexanes to afford N2,N4-bis(4-ethoxycarbonylmethylenedioxyphenyl)-6-ethoxycarbonyl-5-nitro-2,4-pyrimidinediamine (R926566). ¹H NMR (CDCl₃): 10.32 (s, 1H), 7.42 (s, 1H), 7.40 (d, 2H, J= 8.7 Hz), 7.32 (d, 2H, J= 8.7 Hz), 6.93 (d, 2H, J= 8.7 Hz), 6.82 (d, 2H, J= 8.7 Hz), 4.67 (s, 2H), 4.62 (s, 2H), 4.47 (q, 2H, J= 7.5 Hz), 4.30 (m, 4H), 1.42 (t, 3H, J= 6.9 Hz), 1.31 (m, 6H); LCMS: ret. time: 32.10 min.; purity: 100%; MS (m/e): 584 (MH⁺).

7.3.721 N2,N4-Bis[2-(methylthio)-1,3-benzothiaz-6-yl]-5-fluoro-2,4-pyrimidinediamine (R950202)

In like manner to the preparation of N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, the reaction of 2,4-dichloro-5-fluoropyrimidine and 2-(methylthio)-1,3-benzothiazol-6-amine were reacted to prepare N2,N4-bis[2-(methylthio)-1,3-benzothiaz-6-yl]-5-fluoro-2,4-pyrimidinediamine. LCMS: ret. time: 24.98 min.; purity: 84.6%; MS (m/e): 486.80 (MH⁺).

7.3.722 N4-[3-(2-Hydroxyethyleamino)phenyl]-N2-[3-(N-(N-methyl)-piperazino)carbonylmethyleneaminophenyl]-5-fluoro-2,4-pyrimidinediamine (R950240)

In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, N2-(carboxymethyleneaminophenyl)-5-fluoro-N4-[3-(2-hydroxyethylamino)phenyl]-2,4-pyrimidinediamine and N-methylpiperazine were reacted to give N4-[3-(2-hydroxyethylenoxy)phenyl]-N2-[3-(N-(N-methyl)-piperazino)carbonylmethyleneaminophenyl]-5-fluoro-2,4-pyrimidinediamine. LCMS: ret. time: 13.36 min.; purity: 97.6%; MS (m/e): 495.42 (MH⁺).

7.3.723 N4-[3-(2-Hydroxyethyleamino)phenyl]-N2-[3-(N-piperazino)-carbonylmethyleneaminophenyl]-5-fluoro-2,4-pyrimidinediamine (R950241)

In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, N2-(carboxymethyleneaminophenyl)-5-fluoro-N4-[3-(2-hydroxyethyleneamino)phenyl]-2,4-pyrimidinediamine and piperazine were reacted to give N4-[3-(2-hydroxyethyleneamino)phenyl]-N2-[3-(N-piperazino)-carbonylmethyleneaminophenyl]-5-fluoro-2,4-pyrimidinediamine. LCMS: ret. time: 13.21 min.; purity: 100%; MS (m/e): 481.40 (MH⁺).

7.3.724 (±)-N4-(3-Aminophenyl)-5-fluoro-N2-(3-(3-carboxy-3-D,L-N-phtaloylamino)propylenecarbonylaminophenyl)-2,4-pyrimidinediamine (R950251)

N2,N4-Bis(4-aminophenyl)-5-fluoro-2,4-pyrimidinediamine and N-phtaloyl-DL-glutamic anhydride were reacted in DMF to give N4-(3-aminophenyl)-5-fluoro-N2-(3-(3-carboxy-3-D,L-N-phtaloylamino)propylenecarbonylaminophenyl)-2,4-pyrimidinediamine. LCMS: ret. time: 19.41 min.; purity: 95.7%; MS (m/e): 569.98 (MH⁺).

7.3.725 (±)-N4-(3-Aminophenyl)-5-fluoro-N2-[3-(3-carboxy-3-amino)propylenecarbonylaminophenyl]-2,4-pyrimidinediamine (R950255)

(±)-N4-(3-Aminophenyl)-5-fluoro-N2-[3-(3-carboxy-3-D,L-N-phtaloylamino)propylenecarbonylaminophenyl]-2,4-pyrimidinediamine was reacted with hydrazine to give N4-(3-aminophenyl)-5-fluoro-N2-[3-(3-carboxy-3-

amino)propylenecarbonylamino]phenyl]-2,4-pyrimidinediamine. LCMS: ret. time: 11.98 min.; purity: 90.1%; MS (m/e): 440.3 (MH⁺).

7.3.726 5-Methoxycarbonyl-N2,N4-bis[4-(N-pyrrolidino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R926559)

In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, the reaction of 5-ethoxycarbonyl-N2,N4-bis(4-methoxycarbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine with pyrrolidine gave 5-methoxycarbonyl-N2,N4-bis[4-(N-pyrrolidino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. The ethyl ester at 5-position was exchanged to methyl ester in methanol as a solvent. MS (m/e): 575 (MH⁺).

7.3.727 N2,N4-Bis(4-ethoxycarbonylmethyleneoxyphenyl)-5-fluoro-2,4-pyridinediamine (R925565)

In like manner to the preparation of N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, the reaction of 2,4-dichloro-5-fluoropyrimidine with ethyl 4-aminophenoxyacetate gave N2,N4-bis(4-ethoxycarbonylmethyleneoxyphenyl)-5-fluoro-2,4-pyridinediamine. MS (m/e): 485 (MH⁺).

7.3.728 N2-(3-Ethoxycarbonylmethyleneoxyphenyl)-5-ethoxycarbonyl-N4-(3,4-tetrafluoroethylenedioxyphenyl)-2,4-pyrimidinediamine (R926799)

In a manner similar to the preparation of N2-(3-hydroxyphenyl)-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidineamine, the reaction of ethyl 3-aminophenoxyacetate with 2-chloro-5-ethoxycarbonyl-N4-(3,4-tetrafluoroethylenedioxyphenyl)-4-pyrimidineamine gave N2-(3-ethoxycarbonylmethyleneoxyphenyl)-5-ethoxycarbonyl-N4-(3,4-tetrafluoroethylenedioxyphenyl)-2,4-pyrimidinediamine. MS (m/e): 567 (MH⁺).

7.3.729 N4-(3,4-Ethylenedioxyphenyl)-5-fluoro-N2-[3-[N-2-(D)-(+)-biotinylethylamino]carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R926811)

To a solution of D-(+)-biotin and N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-2-hydroxyethylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine in DMF at -20 °C was added diisopropylethylamine and the mixture was shaken for 10 minutes. To this mixture was added benzotriazole-1-yl-oxy-tris(dimethylamino)-

phosphoniumhexafluorophosphate (BOP) and shaken at room temperature for 24 h. The reaction was quenched with water and extracted with ethyl acetate. The ethyl acetate extract was washed with aqueous solution of NaHCO₃ and finally with water. The residue obtained after the removal of solvent was purified by preparative TLC to obtain the desired
5 N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-[N-2-(D)-(+)-biotinylethylamino] carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. LCMS: ret. time: 19.29 min.; purity: 99%; MS (m/e): 682 (M⁺).

7.3.730 5-Fluoro-N4-(3-hydroxyphenyl)-N2[2-(N-methyl-N-2-hydroxyethyl)carbonylbenzofuran-5-yl]-2,4-pyrimidinediamine (R926725)

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In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, the reaction of 5-fluoro-N4-(3-hydroxyphenyl)-N2[2-methoxycarbonylbenzofuran-5-yl]-2,4-pyrimidinediamine with 2-(N-methyl)ethanolamine gave 5-fluoro-N4-(3-hydroxyphenyl)-
15 N2[2-(N-methyl-N-2-hydroxyethyl)carbonylbenzofuran-5-yl]-2,4-pyrimidinediamine. LCMS: ret. time: 14.87 min.; purity: 98%; MS: 438 (MH⁺).

7.3.731 N2,N4-Bis(3-ethoxycarbonylphenyl)-5-fluoro-2,4-pyrimidinediamine (R926228)

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In like manner to the preparation of N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, the reaction of 2,4-dichloro-5-fluoropyrimidine and 3-ethoxycarbonylaniline gave N2,N4-bis(3-ethoxycarbonylphenyl)-5-fluoro-2,4-pyrimidinediamine. LCMS: ret. time: 26.55 min.; purity: 100%; MS (m/e): 425 (MH⁺).

7.3.732 N2-(3-chloro-4-methylbenzyl)-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R908696)

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In a manner similar to the preparation of N2-(3-hydroxyphenyl)-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidineamine, the reaction of 2-chloro-N4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine with 3-chloro-4-methylbenzylamine gave N2-(3-chloro-4-methylbenzyl)-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine. LCMS: ret. time: 25.38 min.; purity: 99 %; MS (m/e): 401 (MH⁺).

7.3.733 (±)-N4-(3,4-Ethylenedioxyphenyl)-5-fluoro-N2-(2-phenylethyl)-2,4-pyrimidinediamine (R908697)

In a manner similar to the preparation of N2-(3-hydroxyphenyl)-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidineamine, the reaction of 2-chloro-N4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine with (±)-2-aminoethylbenzene gave (±)-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(2-phenylethyl)-2,4-pyrimidinediamine. LCMS: ret. time: 23.48 min.; purity: 99 %; MS (m/e): 367 (MH⁺).

7.3.734 N2-(3-Ethoxycarbonylphenyl)-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R925745)

In like manner to preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine and 3-ethoxycarbonylaniline gave N2-(3-ethoxycarbonylphenyl)-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine. ¹H NMR (CDCl₃): δ 8.04 (bs, 1H), 7.94 (bs, 1H), 7.90 (bd, 1H), 7.68 (bd, 1H, J= 7.5 Hz), 7.35 (t, 1H, J= 8.1 Hz), 7.28 (d, 1H, J= 2.4 Hz), 7.07 (s, 1H), 6.93 (dd, 1H, J= 3 and 8.7 Hz), 6.83 (d, 1H, J= 9 Hz), 6.64 (bs, 1H), 4.36 (q, 2H, J= 7.2 Hz), 4.26 (s, 4H), 1.35 (t, 3H, J= 7.5 Hz); ¹⁹F NMR (CDCl₃): -47247; LCMS: ret. time: 15.88.; purity: 100%; MS (m/e): 411 (MH⁺).

7.3.735 N4-(3,4-Difluorophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R920394)

A solution of N-methyl 3-aminophenoxyacetamide (1 equivalent) and 2-chloro-N4-(3,4-difluorophenyl)-5-fluoro-4-pyrimidineamine (1.2 equivalents) in MeOH was shaken in a sealed tube at 100 °C for 24 hours for 24 h. Upon cooling to the room temperature, it was diluted with ethyl acetate. The resulting solid was filtered and washed with a mixture of ethyl acetate: n-hexanes (1:1; v/v) to obtain N4-(3,4-difluorophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. ¹H NMR (DMSO-d₆): δ 10.05 (bs, 1H), 9.83 (bs, 1H), 8.23 (d, 1H, J= 2.7 Hz), 7.98 (m, 2H), 7.52 (m, 1H), 7.39 (m, 1H), 7.20 (m, 3H), 6.60 (m, 1H), 4.37 (s, 2H), 2.63 (d, 3H, J= 3.3 Hz); LCMS: purity: 94%; MS (m/e): 404 (MH⁺).

7.3.736 N4-(4-Chlorophenyl)-5-fluoro-N2-[3-(N-methylamino) carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R920396)

In like manner to preparation of N4-(3,4-difluorophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine the reaction of N-methyl 3-aminophenoxyacetamide with 2-chloro-N4-(4-chlorophenyl)-5-fluoro-4-pyrimidineamine gave N4-(4-chlorophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. ¹H NMR (DMSO-d₆): δ 10.21 (bs, 1H), 10.00 (bs, 1H), 8.26 (d, 1H, J= 4.8 Hz), 8.00 (bd, 1H, J= 4.2 Hz), 7.77 (dd, 2H, J= 2.1 and 7.6 Hz), 7.37 (dd, 2H, J= 2.1 and 7.6 Hz), 7.17 9m, 3H), 8.63 (dd, 1H, J= 1.8 and 8.1 Hz), 4.37 (s, 2H), 2.64 (d, 3H, 4.5 Hz); LCMS: purity: 92%; MS (m/e): 402 (MH⁺).

7.3.736.1 N4-(3,4-Dichlorophenyl)-5-fluoro-N2-[3-(N-methylamino) carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R920397)

In like manner to preparation of N4-(3,4-difluorophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine the reaction of N-methyl 3-aminophenoxyacetamide with 2-chloro-N4-(3,4-dichlorophenyl)-5-fluoro-4-pyrimidineamine gave N4-(3,4-dichlorophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. ¹H NMR (DMSO-d₆): δ 10.02 (bs, 1H), 9.76 (bs, 1H), 8.24 (d, 1H, J= 4.2 Hz), 8.08 (m, 1H), 7.97 (bd, 1H, J= 4.8 Hz), 7.77 (m, 1H), 7.55 (d, 1H, J= 8.7 Hz), 7.18 (m, 3H), 6.58 (m, 1H), 4.36 (s, 1H), 2.63 (d, 1H, J= 2.7 Hz); LCMS: purity: 91%; MS: 434 (MH⁺).

7.3.737 5-Fluoro-N4-(5-methylpyridin-2-yl)-N2-[3-(N-methylamino) carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R920398)

In like manner to preparation of N4-(3,4-difluorophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine the reaction of N-methyl 3-aminophenoxyacetamide with 2-chloro-5-fluoro-N4-(5-methylpyridin-2-yl)-4-pyrimidineamine gave 5-fluoro-N4-(5-methylpyridin-2-yl)-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. ¹H NMR (DMSO-d₆): δ 11.35 (bs, 1H), 10.70 (bs, 1H), 8.58 (s, 1H), 8.42 (d, 1H, J= 3.0 Hz), 8.12 (bd, 1H, J= 9.3 Hz), 8.03 (bd, 1H, J= 4.2 Hz), 7.82 (d, 1H, J= 8.7 Hz), 7.56 (s, 1H), 7.30 (bdd, 1H, J= 8.1

Hz), 7.19 (t, 1H, J= 8.1 Hz), 6.55 (dd, 1H, J= 1.8 and 8.1 Hz), 4.41 (s, 2H), 2.63 (d, 3H, J= 3.6 Hz), 2.36 (s, 3H); LCMS: purity: 99%; MS (m/e): 382 (M⁺).

7.3.738 5-Fluoro-N4-(6-methylpyridin-2-yl)-N2-[3-(N-methylamino) carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R920399)

In like manner to preparation of N4-(3,4-difluorophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine the reaction of N-methyl 3-aminophenoxyacetamide with 2-chloro-5-fluoro-N4-(6-methylpyridin-2-yl)-4-pyrimidineamine gave 5-fluoro-N4-(6-methylpyridin-2-yl)-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. ¹H NMR (DMSO-d₆): δ 10.00 (bs, 1H), 9.60 (bs, 1H), 8.25 (s, 1H), 7.95 (m, 3H), 7.30 (s, 1H), 7.10 (m, 3H), 6.55 (d, 1H, J= 7.2 Hz), 4.40 (s, 2H), 2.62 (d, 3H, J= 3.6 Hz), 2.45 (s, 3H); LCMS: purity: 92%; MS (m/e): 383 (MH⁺).

7.3.739 N4-(5-Chloropyridin-2-yl)-5-fluoro-N2-[3-(N-methylamino) carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R920405)

In like manner to preparation of N4-(3,4-difluorophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine the reaction of N-methyl 3-aminophenoxyacetamide with 2-chloro-N4-(5-chloropyridin-2-yl)-5-fluoro-4-pyrimidineamine gave N4-(5-chloropyridin-2-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. ¹H NMR (DMSO-d₆): δ 10.04 (bs, 1H), 9.53 (bs, 1H), 8.40 (d, 1H, J= 2.4 Hz), 8.22 (m, 2H), 7.88 (bd, 1H, J= 4.5 Hz), 7.86 (dd, 1H, J= 2.4 and 8.7 Hz), 7.40 (d, 1H, J= 1.8 Hz), 7.19 (m, 2H), 6.51 (bdd, 1H, J= 1.2 and 9 Hz), 4.38 (s, 2H), 2.64 (d, 3H, J= 3.3 Hz); LCMS: purity: 95%; MS (m/e): 403 (MH⁺).

7.3.740 N4-(6-Chloropyridin-3-yl)-5-fluoro-N2-[3-(N-methylamino) carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R920406)

In like manner to preparation of N4-(3,4-difluorophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine the reaction of N-methyl 3-aminophenoxyacetamide with 2-chloro-N4-(6-chloropyridin-3-yl)-5-fluoro-4-pyrimidineamine gave N4-(6-chloropyridin-3-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. ¹H NMR (DMSO-d₆):

δ 9.72 (s, 1H), 9.38 (s, 1H), 8.93 (t, 1H, J= 3.0 Hz), 8.28 (m, 1H), 8.18 (d, 1H, J= 3.6 Hz), 7.95 (m, 1H), 7.45 (d, 1H, J= 8.7 Hz), 7.39 (m, 1H), 7.21 (m, 1H), 7.14 (t, 1H, J= 4.8 Hz), 6.50 (bdd, 1H, J= 7.8 Hz), 4.4 (s, 2H), 2.63 (d, 3H); LCMS: purity: 100%; MS (m/e): 403 (MH⁺).

5 **7.3.741 5-Fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-N4-(4-methylpyridin-2-yl)-2,4-pyrimidinediamine (R927016)**

In like manner to preparation of N4-(3,4-difluorophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine the reaction of N-methyl 3-aminophenoxyacetamide with 2-chloro-5-fluoro-N4-(4-methylpyridin-2-yl)-4-pyrimidineamine gave 5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-N4-(4-methylpyridin-2-yl)-2,4-pyrimidinediamine. LCMS: purity: 95%; MS (m/e): 383 (MH⁺).

15 **7.3.742 5-Fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-N4-(3-trifluoromethoxyphenyl)-2,4-pyrimidinediamine (R920407)**

In like manner to preparation of N4-(3,4-difluorophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine the reaction of N-methyl 3-aminophenoxyacetamide with 2-chloro-5-fluoro-N4-(3-trifluoromethylphenyl)-4-pyrimidineamine gave 5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-N4-(3-trifluoromethoxyphenyl)-2,4-pyrimidinediamine. ¹H NMR (DMSO-d₆): δ 9.835 (bs, 1H), 9.54 (bs, 1H), 8.20 (d, 1H, J= 3.6 Hz), 7.94 (m, 2H), 7.78 (bs, 1H), 7.43 (t, 1H, J= 8.4 Hz), 7.25 (m, 2H), 7.15 (t, 1H, J= 7.5 Hz), 7.03 (bd, 1H, J= 9.3 Hz), 6.55 (bd, 1H, J= 7.5 Hz), 4.36 (s, 2H), 2.63 (d, 3H, J= 4.5 Hz); LCMS: purity: 91%; MS (m/e): 452 (MH⁺).

25 **7.3.743 N4-(3,4-Difluoromethylenedioxyphenyl)-5-fluoro- N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R920408)**

In like manner to preparation of N4-(3,4-difluorophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine the reaction of N-methyl 3-aminophenoxyacetamide with 2-chloro-N4-(3,4-difluoromethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine gave N4-(3,4-difluoromethylenedioxyphenyl)-5-fluoro- N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. ¹H NMR (DMSO-d₆): δ 9.91 (bs, 1H), 9.64 (bs, 1H), 8.19 (d, 1H, J= 3.9 Hz), 8.03 (s, 1H), 7.96 (bd, 1H, J= 4.8 Hz), 7.46 (m, 1H), 7.36 (d, 1H, J= 8.7 Hz), 7.27 (bs, 1H), 7.17 (m, 2H), 6.57 (bdd, 1H,

J= 7.2 Hz), 4.36 (s, 1H), 2.62 (d, 3H, J= 4.5 Hz); LCMS: purity: 96%; MS (m/e): 448 (MH⁺).

7.3.744 N4-(3-Chloro-4-trifluoromethoxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R920410)

In like manner to preparation of N4-(3,4-difluorophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine the reaction of N-methyl 3-aminophenoxyacetamide with 2-chloro-N4-(3-chloro-4-trifluoromethoxyphenyl)-5-fluoro-4-pyrimidineamine gave N4-(3-chloro-4-trifluoromethoxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. ¹H NMR (CD₃OD): δ 8.08 (d, 1H, J= 5.4 Hz), 7.99 (d, 1H, J= 3.6 Hz), 7.67 (dd, 1H, J= 2.4 and 9.0 Hz), 7.40 (m, 3H), 7.06 (m, 2H), 6.92 (dd, 1H, J= 2.4 and 8.4 Hz), 4.44 (s, 2H), 2.80 (s, 3H); ¹⁹F NMR (CD₃OD): - 16973 and - 45983; LCMS: purity: 96%; MS (m/e): 486 (MH⁺).

7.3.745 N4-(4-Ethoxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R926827)

In like manner to preparation of N4-(3,4-difluorophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine the reaction of N-methyl 3-aminophenoxyacetamide with 2-chloro-N4-(4-ethoxyphenyl)-5-fluoro-4-pyrimidineamine gave N4-(4-ethoxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. LCMS: purity: 96%; MS: 412 (MH⁺).

7.3.746 N4-(3,4-Ethylenedioxyphenyl)-5-fluoro-N2-[4-methoxy-3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R926828)

In like manner to preparation of N4-(3,4-difluorophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine the reaction of N-methyl 3-amino-6-methoxyphenoxyacetamide with 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine gave N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[4-methoxy-3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. ¹H NMR (CD₃OD): δ 7.83 (s, 1H), 7.80 (d, 1H, J= 4.2 Hz), 7.30 (d, 1H, 2.4 Hz), 7.23 (d, 1H, J= 2.4 Hz), 7.06 (m, 2H), 6.90 (d, 1H, J= 5.7 Hz), 6.73 (d, 1H, J= 5.2

Hz), 4.32 (s, 2H), 4.22 (s, 4H), 3.86 (s, 3H), 2.83 (s, 3H); LCMS: purity: 97%; MS (m/e): 455 (MH⁺).

7.3.747 5-Fluoro-N4-(3-hydroxyphenyl)-N2-[4-methoxy-3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R926829)

In like manner to preparation of N4-(3,4-difluorophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine the reaction of N-methyl 3-amino-4-methoxyphenoxyacetamide with 2-chloro-5-fluoro-N4-(3-hydroxyphenyl)-4-pyrimidineamine gave 5-fluoro-N4-(3-hydroxyphenyl)-N2-[4-methoxy-3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. ¹H NMR (CD₃OD): δ 7.86 (d, 1H, J= 4.2 Hz), 7.35 (d, 1H, J= 2.4 Hz), 7.19 (m, 1H), 7.12 (m, 3H), 6.93 (d, 1H, J= 8.7 Hz), 6.52 (m, 1H), 4.37 (s, 2H), 3.85 (s, 3H), 2.82 (s, 3H); ¹⁹F NMR (CD₃OD): - 47650; LCMS: purity: 100%; MS: 414 (MH⁺).

7.3.748 N4-(3-Chlorophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R926832)

In like manner to preparation of N4-(3,4-difluorophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine the reaction of 3 N-methyl 3-aminophenoxyacetamide with 2-chloro-N4-(3-chlorophenyl)-5-fluoro-4-pyrimidineamine gave N4-(3-chlorophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. ¹H NMR (DMSO-d₆): δ 10.12 (s, 1H), 9.93 (s, 1H), 8.27 (d, 1H, J= 4.2 Hz), 7.98 (d, 1H, J= 4.9 Hz), 7.85 (s, 1H), 7.73 (d, 1H, J= 8.1 Hz), 7.35 (t, 1H, J= 8.4 Hz), 7.19 (m, 3H), 6.62 (m, 1H), 4.36 (s, 2H), 2.63 (d, 3H, J= 4.2 Hz); LCMS: purity: 95%; MS: 402 (MH⁺).

7.3.749 5-Fluoro-N4-(3-methoxy-5-trifluoromethylphenyl)-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R926833)

In like manner to preparation of N4-(3,4-difluorophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine the reaction of N-methyl 3-aminophenoxyacetamide with 2-chloro-5-fluoro-N4-(3-methoxy-5-trifluoromethylphenyl)-4-pyrimidineamine gave 5-fluoro-N4-(3-methoxy-5-trifluoromethylphenyl)-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. LCMS: purity: 95%; MS (m/e): 466 (MH⁺).

7.3.750 5-Fluoro-N4-(3-hydroxy-4-methoxyphenyl)-N2-[3-(N-methylamino) carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R926834)

In like manner to preparation of N4-(3,4-difluorophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine the reaction of N-methyl 3-aminophenoxyacetamide with 2-chloro-5-fluoro-N4-(3-hydroxy-4-methoxyphenyl)-4-pyrimidineamine gave 5-fluoro-N4-(3-hydroxy-4-methoxyphenyl)-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. ¹H NMR (DMSO-d₆): δ 9.70 (bs, 2H), 8.12 (d, 1H, J = 4.8 Hz), 7.96 (m, 1H), 7.12 (m, 5H), 6.85 (d, 1H, J = 8.7 Hz), 6.57 (bd, 1H, J = 8.1 Hz), 4.35 (s, 2H), 3.74 (s, 3H), 2.63 (d, 3H, J = 4.5 Hz); LCMS: purity: 99%; MS (m/e): 414 (MH⁺).

7.3.751 5-Fluoro-N4-(4-methoxy-3-trifluoromethylphenyl)-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R926835)

In like manner to preparation of N4-(3,4-difluorophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine the reaction of N-methyl 3-aminophenoxyacetamide with 2-chloro-5-fluoro-N4-(4-methoxy-3-trifluoromethylphenyl)-4-pyrimidineamine gave 5-fluoro-N4-(4-methoxy-3-trifluoromethylphenyl)-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. ¹H NMR (DMSO-d₆): δ 9.9 Bs, 1H), 9.62 (bs, 1H), 8.17 (d, 1H, J = 4.2 Hz), 8.04 (bdd, 1H, J = 7.2 Hz), 7.82 (t, 1H, 2.7 Hz), 7.18 (m, 3H), 7.11 (t, 1H, J = 8.1 Hz), 6.55 (bd, 1H, J = 6.9 Hz); 4.33 (s, 2H), 3.86 (s, 3H), 2.61 (d, 3H, J = 4.0 Hz); LCMS: purity: 93%; MS: 466 (MH⁺).

7.3.752 5-Fluoro-N4-(4-fluoro-3-trifluoromethylphenyl)-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R926838)

In like manner to preparation of N4-(3,4-difluorophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine the reaction of N-methyl 3-aminophenoxyacetamide with 2-chloro-5-fluoro-N4-(4-fluoro-3-trifluoromethylphenyl)-4-pyrimidineamine gave 5-fluoro-N4-(4-fluoro-3-trifluoromethylphenyl)-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. ¹H NMR (DMSO-d₆): δ 9.80 (s, 1H), 9.44 (s, 1H), 8.25 (m, 1H), 8.18 (d, 1H, J = 3.9 Hz), 8.00 (m, 1H), 7.97 (m, 1H), 7.47 (t, 1H, J = 9.6 Hz), 7.26 (s, 1H), 7.21

(m, 1H), 7.11 (t, 1H, J= 8.4 Hz), 6.51 (bd, 1H, J= 9.9 Hz), 4.34 (s, 2H), 2.62 (d, 3H, J= 4.8 Hz); LCMS: purity: 88%; MS: 454 (MH⁺).

7.3.753 N4-(3-Chloro-4-methylphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R926839)

In like manner to preparation of N4-(3,4-difluorophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine the reaction of N-methyl 3-aminophenoxyacetamide with 2-chloro-N4-(3-chloro-4-methylphenyl)-4-pyrimidineamine gave N4-(3-chloro-4-methylphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. ¹H NMR (DMSO-d₆): δ 9.69 (s, 1H), 9.52 (s, 1H), 8.16 (d, 1H, J= 4.2 Hz), 7.96 (bs, 1H), 7.81 (d, 1H, J= 2.1 Hz), 7.67 (bd, 1H, J= 8.4 Hz), 7.26 (m, 3H), 7.15 (t, 1H, J= 8.1 Hz), 6.54 (bd, 1H, J= 7.2 Hz), 4.34 (s, 2H), 2.63 (d, 3H, J= 4.2 Hz), 2.27 (s, 3H); LCMS: purity: 80%; MS (m/e): 415 (M⁺).

7.3.754 N4-(2-Chloro-5-methylphenyl)-5-fluoro-N2-[3-(N-methylamino) carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R926840)

In like manner to preparation of N4-(3,4-difluorophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine the reaction of N-methyl 3-aminophenoxyacetamide with 2-chloro-N4-(2-chloro-5-methylphenyl)-4-pyrimidineamine gave N4-(2-chloro-5-methylphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. ¹H NMR (DMSO-d₆): δ 9.80 (bs, 2H), 8.21 (d, 1H, J= 4.8 Hz), 7.92 (d, 1H, J= 4.8 Hz), 7.46 (m, 1H), 7.31 (m, 2H), 7.04 (m, 2H), 6.53 (bd, 1H, J= 8.1 Hz), 4.30 (s, 1H), 2.18 (s, 3H); LCMS: purity: 93%; MS (m/e): 416 (MH⁺).

7.3.755 N4-(3,4-Ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-isopropylamino) carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R926830)

The reaction of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(ethoxycarbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine with isopropylamine (5 equivalents) in the presence of diisopropylethylamine (5 equivalents) in MeOH in a sealed tube at 80 °C for 24 hours gave N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-isopropylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. ¹H NMR (DMSO-

d6): δ 9.15 (s, 1H), 8.04 (d, 1H, J = 4.2 Hz), 7.77 (d, 1H, J = 7.5 Hz), 7.28 (m, 4H), 7.08 (t, 1H, J = 8.1 Hz), 6.78 (d, 1H, J = 8.7 Hz), 6.45 (dd, 1H, J = 1.8 and 7.8 Hz), 4.30 (s, 2H), 4.20 (s, 4H), 3.92 (m, 1H), 1.06 (d, 6H, J = 6.6 Hz); LCMS: purity: 95%; MS (m/e): 454 (MH^+).

5 **7.3.756 N2-[3-(N-Cyclopropylamino)carbonylmethyleneoxyphenyl]-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R926848)**

In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-isopropylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, the reaction of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(ethoxycarbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine with cyclopropylamine gave 5-fluoro-N4-(3,4-ethylenedioxyphenyl)-N2-[3-(N-cyclopropylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. 1H NMR (DMSO- d_6): δ 9.17 (bs, 2H), 8.05 (m, 2H), 7.27 (m, 4H), 7.08 (t, 1H, J = 8.1 Hz), 7.67 (d, 1H, J = 8.7 Hz), 6.42 (dd, 1H, J = 2.4 and 8.1 Hz), 4.3 (s, 2H), 4.2 (bs, 4H), 2.65 (m, 1H), 0.6 (m, 2H), 0.45 (m, 2H); LCMS: purity: 91%; MS (m/e): 452 (MH^+).

15 **7.3.757 N4-(4-Cyano-3-methylphenyl)-5-fluoro-N2-[3-(N-methylamino) carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R926851)**

In like manner to preparation of N4-(3,4-difluorophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine the reaction of N-methyl 3-aminophenoxyacetamide with 2-chloro-N4-(4-cyano-3-methylphenyl)-4-pyrimidineamine gave N4-(4-cyano-3-methylphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. 1H NMR (DMSO- d_6): δ 9.7 (s, 1H), 9.40 (s, 1H), 8.2 (s, 1H), 8.00-7.50 (m, 3H), 7.40-7.00 (m, 3H), 6.50 (bm, 1H), 4.35 (s, 2H), 2.60 (s, 3H), 2.35 (s, 3H); LCMS: purity: 91%; MS (m/e): 407 (MH^+).

25 **7.3.758 5-Fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-N4-[3-(tetrazol-5-yl)phenyl]-2,4-pyrimidinediamine (R926855)**

In like manner to preparation of N4-(3,4-difluorophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine the reaction of N-methyl 3-aminophenoxyacetamide with 2-chloro-5-fluoro-N4-[3-(1H-tetrazol-5-yl)phenyl]-4-pyrimidineamine gave 5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-N4-[3-(tetrazol-5-yl)phenyl]-2,4-pyrimidinediamine. 1H NMR (DMSO- d_6): δ 10.04 (bs, 1H), 9.65 (bs, 1H), 8.35 (s, 1H), 8.23 (d, 1H, J = 3.9 Hz), 8.00 (bd, 1H, J = 6.6 Hz), 7.91 (bd,

J= 3.6 Hz), 7.77 (d, 1H, J= 8.1 Hz), 7.57 (t, 1H, J= 8.1 Hz), 7.23 (m, 2H), 6.95 (t, 1H, J= 8.4 Hz), 6.46 (bdd, 1H, J= 1.8 and 8.1 Hz), 4.22 (s, 2H), 2.62 (d, 3H, 4.2 Hz); LCMS: purity: 83%; MS (m/e): 436 (MH⁺).

7.3.759 5-Fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-N4-(N-methylphthalimido-4-yl)-2,4-pyrimidinediamine (R926856)

In like manner to preparation of N4-(3,4-difluorophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine the reaction of N-methyl 3-aminophenoxyacetamide with 2-chloro-5-fluoro-N4-(N-methylphthalimido-4-yl)-4-pyrimidineamine gave 5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-N4-(N-methylphthalimido-4-yl)-2,4-pyrimidinediamine. ¹H NMR (DMSO-d₆): δ 9.95 (s, 1H), 9.44 (s, 1H), 8.29 (m, 1H), 8.25 (m, 1H), 8.18 (d, 1H, J= 1.8 Hz), 7.88 (bd, 1H, J= 4.5 Hz), 7.75 (d, 1H, J= 6.6 Hz), 7.38 (bs, 1H), 7.22 (bd, 1H, J= 8.1 Hz), 7.14 (t, 1H, J= 7.8 Hz), 6.50 (dd, 1H, J= 1.8 and 9.0 Hz), 4.28 (s, 2H), 2.99 (s, 3H), 2.60 (d, 3H, J= 4.5 Hz); LCMS: purity: 92%; MS (m/e): 451 (MH⁺).

7.3.760 N4-(2,5-Dimethoxy-4-chlorophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R926859)

In like manner to preparation of N4-(3,4-difluorophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine the reaction of N-methyl 3-aminophenoxyacetamide with N4-(2,5-dimethoxy-4-chlorophenyl)-2-chloro-5-fluoro-4-pyrimidineamine gave N4-(2,5-dimethoxy-4-chlorophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. ¹H NMR (CD₃OD): δ 8.05 (d, 1H, J= 5.4 Hz), 7.29 (s, 1H), 7.24 (t, 1H, J= 8.1 Hz), 7.18 (s, 1H), 7.02 (t, 1H, J= 2.1 Hz), 6.92 (dd, 1H, J= 1.8 and 8.1 Hz), 6.83 (dd, 1H, J= 2.4 and 8.4 Hz), 4.29 (s, 2H), 3.81 (s, 3H), 3.59 (s, 3H), 2.81 (s, 3H); LCMS: purity: 96%; MS (m/e): 460 (MH⁻); 462 (MH⁻).

7.3.761 5-Fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-N4-(3-methoxycarbonyl-5-trifluoromethylphenyl)-2,4-pyrimidinediamine (R926862)

In like manner to preparation of N4-(3,4-difluorophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine the reaction of N-methyl 3-aminophenoxyacetamide with 2-chloro-5-fluoro-N4-(3-methoxycarbonyl-5-

trifluoromethylphenyl)-4-pyrimidineamine gave 5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-N4-(3-methoxycarbonyl-5-trifluoromethylphenyl)-2,4-pyrimidinediamine. ¹H NMR (DMSO-d₆): δ 9.95 (s, 1H), 9.41 (s, 1H), 8.57 (s, 1H), 8.33 (s, 1H), 8.23 (d, 1H, J= 3 Hz), 7.83 (s and d, 2H), 7.22 (m, 2H), 7.02(t, 1H, J= 8.7 Hz), 6.48 (1H, J= 2.4 and 7.5 Hz), 4.27 (s, 2H), 3.80 (s, 3H), 2.60 (d, 3H, J= 4.8 Hz); ¹⁹F NMR (DMSO-d₆): - 17446; LCMS: purity: 94%; MS (m/z): 494 (MH⁺).

7.3.762 5-Fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-N4-[3-(2-phenyl-1,3,4-oxadiazol-5-yl)phenyl]-2,4-pyrimidinediamine (R926870)

In like manner to preparation of N4-(3,4-difluorophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine the reaction of N-methyl 3-aminophenoxyacetamide with 2-chloro-5-fluoro-N4-[3-(2-phenyl-1,3,4-oxadiazol-5-yl)phenyl]-4-pyrimidineamine gave 5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-N4-[3-(2-phenyl-1,3,4-oxadiazol-5-yl)phenyl]-2,4-pyrimidinediamine. LCMS: purity: 86%; MS (m/e): 512 (MH⁺).

7.3.763 N4-[3-(2-(3-Chlorophenyl)-1,3,4-oxadiazol-5-yl)phenyl]-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R926871)

In like manner to preparation of N4-(3,4-difluorophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine the reaction of N-methyl 3-aminophenoxyacetamide with 2-chloro-5-fluoro-N4-[3-(2-(3-chlorophenyl)-1,3,4-oxadiazol-5-yl)phenyl]-4-pyrimidineamine gave N4-[3-(2-(3-chlorophenyl)-1,3,4-oxadiazol-5-yl)phenyl]-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. LCMS: purity: 100%; MS (m/e): 546 (MH⁺).

7.3.764 5-Fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-N4-[4-trifluoromethoxyphenyl]-2,4-pyrimidinediamine (R926879)

In like manner to preparation of N4-(3,4-difluorophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine the reaction of N-methyl 3-aminophenoxyacetamide with 2-chloro-5-fluoro-N4-(4-trifluoromethoxyphenyl)-4-pyrimidineamine gave 5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-N4-[4-trifluoromethoxyphenyl]-2,4-pyrimidinediamine. ¹H NMR (DMSO-d₆): δ 10.05 (bs, 1H), 9.74 (bd, 1H, J= 1.5 Hz), 8.22 (d, 1H, J= 4.2 Hz), 7.99 (bd, 1H, J= 4.5 Hz), 7.86 (m,

2H), 7.32 (d, 2H, J= 8.1 Hz), 7.26 (s, 1H), 7.16 (m, 2H), 6.58 (m, 1H), 4.36 (s, 2H), 2.65 (bd, 3H); LCMS: purity: 92%; MS (m/e): 452 (MH⁺).

7.3.765 5-Fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-N4-[4-trifluoromethylphenyl]-2,4-pyrimidinediamine (R926880)

In like manner to preparation of N4-(3,4-difluorophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine the reaction of N-methyl 3-aminophenoxyacetamide with 2-chloro-5-fluoro-N4-(4-trifluoromethylphenyl)-4-pyrimidineamine gave 5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-N4-[4-trifluoromethylphenyl]-2,4-pyrimidinediamine. ¹H NMR (DMSO-d₆): δ 10.10 (bs, 1H), 9.72 (d, 1H, J= 1.2 Hz), 8.26 (d, 1H, J= 4.2 Hz), 8.00 (m, 3H), 7.65 (d, 2H, J= 8.1 Hz), 7.31 (bs, 1H), 7.17 (d, 2H, J= 5.4 Hz), 6.59 (m, 1H), 4.36 (s, 2H), 2.62 (d, 3H, J= 4.8 Hz); LCMS: purity: 92%; MS (m/e): 436 (MH⁺).

7.3.766 N4-(4-Chloro-3-trifluoromethylphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R926881)

In like manner to preparation of N4-(3,4-difluorophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine the reaction of N-methyl 3-aminophenoxyacetamide with 2-chloro-N4-(4-chloro-3-trifluoromethylphenyl)-5-fluoro-4-pyrimidineamine gave N4-(4-chloro-3-trifluoromethylphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. ¹H NMR (DMSO-d₆): δ 10.20 (bs, 1H), 9.81 (bs, 1H), 8.28 (d, 1H, J= 3.9 Hz), 8.23 (bdd, 1H, J= 8.7 Hz), 8.11 (d, 1H, J= 2.4 Hz), 7.98 (bd, 1H, J= 4.5 Hz), 7.65 (d, 1H, J= 8.7 Hz), 7.17 (m, 3H), 6.59 (m, 1H), 4.35 (s, 2H), 2.63 (d, 3H, J= 4.2 Hz); LCMS: purity: 87%; MS (m/e): 470 (MH⁺).

7.3.767 5-Fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-N4-(quinolin-6-yl)-2,4-pyrimidinediamine (R926883)

In like manner to preparation of N4-(3,4-difluorophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine the reaction of 3 N-methyl 3-aminophenoxyacetamide with 2-chloro-5-fluoro-N4-(quinolin-6-yl)-4-pyrimidineamine gave 5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-N4-(quinolin-6-yl)-2,4-pyrimidinediamine. ¹H NMR (DMSO-d₆): δ 10.17 (bs, 1H), 9.83 (s, 1H), 8.24 (d, 1H, J= 4.8 Hz), 8.17 (m, 1H), 7.94 (m, 2H), 7.86 (m, 1H), 7.39 (d, 1H, J= 9.3

Hz), 7.25 (s, 1H), 7.16 (m, 2H), 6.60 (m, 1H), 6.50 (d, 1H, J = 9.6 Hz), 4.32 (s, 2H), 2.60 (d, 3H, J = 3.6 Hz); LCMS: purity: 98%; MS (m/e): 436 (MH⁺).

7.3.768 5-Fluoro-N4-(2-methoxypyridin-5-yl)-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R926886)

In like manner to preparation of N4-(3,4-difluorophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine the reaction of N-methyl 3-aminophenoxyacetamide with 2-chloro-5-fluoro-N4-(2-methoxypyridin-5-yl)-4-pyrimidineamine gave 5-fluoro-N4-(2-methoxypyridin-5-yl)-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. ¹H NMR (DMSO-d₆): δ 9.36 (bs, 1H), 9.19 (s, 1H), 8.59 (d, 1H, J = 3 Hz), 8.05 (m, 3H), 7.38 (m, 1H), 7.24 (bd, 1H, J = 8.1 Hz), 7.08 (t, 1H, J = 8.4 Hz), 6.79 (d, 1H, J = 8.7 Hz), 6.46 (dd, 1H, J = 2.4 and 7.8 Hz), 4.34 (s, 2H), 3.82 (s, 3H), 2.63 (d, 3H, J = 4.5 Hz); LCMS: purity: 95%; MS (m/e): 399 (MH⁺).

7.3.769 5-Fluoro-N4-[2-(2-hydroxyethyleneoxy)pyridin-5-yl]-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R927023)

In like manner to preparation of N4-(3,4-difluorophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine the reaction of N-methyl 3-aminophenoxyacetamide with 2-chloro-5-fluoro-N4-[2-(2-hydroxyethyleneoxy)pyridin-5-yl]-4-pyrimidineamine gave 5-fluoro-N4-[2-(2-hydroxyethyleneoxy)pyridin-5-yl]-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. ¹H NMR (DMSO-d₆): δ 9.65 (bs, 1H), 9.45 (bs, 1H), 8.55 (s, 1H), 8.12 (d, 1H, J = 3.6 Hz), 7.99 (m, 2H), 7.28 (m, 1H), 7.19 (m, 2H), 7.11 (t, 1H, J = 8.4 Hz), 6.81 (d, 1H, J = 8.7 Hz), 6.52 (m, 2H), 4.35 (s, 2H), 4.23 (t, 2H, J = 5.1 Hz), 3.69 (t, 2H, J = 4.5 Hz), 2.63 (d, 3H, J = 2.7 Hz); LCMS: purity: 95%; MS (m/e): 429 (MH⁺).

7.3.770 N4-(2,6-Dimethoxypyridin-3-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R920404)

In like manner to preparation of N4-(3,4-difluorophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine the reaction of N-methyl 3-aminophenoxyacetamide with 2-chloro-N4-(2,6-dimethoxypyridin-3-yl)-5-fluoro-4-pyrimidineamine gave N4-(2,6-dimethoxypyridin-3-yl)-5-fluoro-N2-[3-(N-

methylamino)carbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine. ¹H NMR (DMSO-d₆): δ 9.05 (d, 1H, J= 1.8 Hz), 8.62 (s, 1H), 8.01 (d, 1H, J= 3.6 Hz), 7.91 (bd, 1H, J= 4.8 Hz), 7.77 (m, 1H), 7.18 (m, 2H), 6.96 (t, 1H, J= 8.1 Hz), 6.40 (d, 2H, J= 8.1 Hz), 4.29 (s, 2H), 3.86 (s, 3H), 3.85 (s, 3H), 2.63 (d, 3H, J= 4.5 Hz); LCMS: purity: 86%; MS (m/e): 429 (MH⁺).

7.3.771 N4-(4-Chloro-3-methoxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R927042)

In like manner to preparation of N4-(3,4-difluorophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine the reaction of N-methyl 3-aminophenoxyacetamide with 2-chloro-N4-(4-chloro-3-methoxyphenyl)-5-fluoro-4-pyrimidineamine gave N4-(4-chloro-3-methoxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. ¹H NMR (DMSO-d₆): δ 9.89 (bs, 1H), 9.66 (bs, 1H), 8.20 (d, 1H, J= 4.2 Hz), 7.95 (bd, 1H), 7.48 (m, 2H), 7.33 (d, 1H, J= 9.1 Hz), 7.26 (bs, 1H), 7.17 (m, 2H), 6.57 (bd, 1H, J= 7.8 Hz), 4.34 (s, 2H), 3.72 (s, 3H), 2.62 (d, 3H); LCMS: purity: 97%; MS (m/e): 432 (MH⁺).

7.3.772 N4-(3-Chloro-4-trifluoromethoxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine (R920411)

A solution of 2-chloro-N4-(3-chloro-4-trifluoromethoxyphenyl)-5-fluoro-4-pyrimidineamine (1.1 equivalents) and 3-hydroxyaniline (1 equivalent) in a sealed tube was heated at 100 °C for 24 hours. The resulting solution was diluted with EtOAc and the solid obtained was filtered, washed with a mixture of EtOAc:n-hexanes (1:1; v/v), dried and analyzed to give N4-(3-chloro-4-trifluoromethoxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidineamine. ¹H NMR (CD₃OD): δ 8.02 (d, 1H, J= 5.1 Hz), 7.98 (d, 1H, J= 3.0 Hz), 7.72 (dd, 1H, J= 3.0 and 9.3 Hz), 7.42 (dd, 1H, J= 1.2 and 9.0 Hz), 7.22 (t, 1H, J= 8.4 Hz), 6.85 (m, 2H), 6.73 (dd, 1H, J= 2.4 and 8.7 Hz); ¹⁹F NMR (CD₃OD): - 16967 and - 46027; LCMS: purity: 97%; MS (m/e): 415 (MH⁺).

7.3.773 5-Fluoro-N2-(3-hydroxyphenyl)-N4-[3-(3-phenyl-1,3,4-oxadiazol-5-yl)phenyl]-2,4-pyrimidinediamine (R926866)

In like manner to the preparation of N4-(3-chloro-4-trifluoromethoxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidineamine, the reaction of 3-hydroxyaniline with 2-chloro-5-fluoro-N4-[3-(2-phenyl-1,3,4-oxadiazol-5-yl)phenyl]-4-pyrimidineamine gave

5-fluoro-N2-(3-hydroxyphenyl)-N4-[3-(2-phenyl-1,3,4-oxadiazol-5-yl)phenyl]-2,4-pyrimidinediamine. ¹H NMR (CD₃OD): δ 7.72 (bs, 1H), 7.96 (bd, 3H), 7.85 (m, 2H), 7.56 (m, 4H), 7.14 (d, 1H, J= 2.1 Hz), 6.91 (m, 2H), 6.28 (dd, 1H, J= 1.8 and 6.9 Hz); LCMS: purity: 80%; MS (m/e): 441 (MH⁺).

5 **7.3.774 N4-(3,4-Difluoromethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine (R926794)**

In like manner to the preparation of N4-(3-chloro-4-trifluoromethoxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidineamine, the reaction of 3-hydroxyaniline with 2-chloro-N4-(3,4-difluoromethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine gave N4-(3,4-difluoromethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine. LCMS: purity: 85%; MS (m/e): 377 (MH⁺).

7.3.775 5-Fluoro-N2-(3-hydroxyphenyl)-N4-(3-trifluoromethoxyphenyl)-2,4-pyrimidinediamine (R926885)

In like manner to the preparation of N4-(3-chloro-4-trifluoromethoxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidineamine, the reaction of 3-hydroxyaniline with 2-chloro-5-fluoro-N4-(3-trifluoromethoxyphenyl)-4-pyrimidineamine gave 5-fluoro-N2-(3-hydroxyphenyl)-N4-(3-trifluoromethoxyphenyl)-2,4-pyrimidinediamine. ¹H NMR (DMSO-d₆): δ 9.99 (bs, 1H), 9.61 (bs, 1H), 8.21 (d, 1H, J= 4.2 Hz), 7.93 (bd, 1H, J= 7.5 Hz), 7.78 (s, 1H), 7.43 (t, 1H, J= 8.4 Hz), 7.03 (m, 4H), 6.43 (m, 1H); ¹⁹F NMR (DMSO-d₆): -16097; LCMS: purity: 85%; MS (m/e): 381 (MH⁺).

7.3.776 N4-(2,6-Dimethoxypyridin-3-yl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine (R926887)

In like manner to the preparation of N4-(3-chloro-4-trifluoromethoxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidineamine, the reaction of 3-hydroxyaniline with 2-chloro-N4-(2,6-dimethoxypyridin-3-yl)-5-fluoro-4-pyrimidineamine gave N4-(2,6-dimethoxypyridin-3-yl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine. ¹H NMR (DMSO-d₆): δ 9.98 (bs, 2H), 8.20 (d, 1H, J= 5.4 Hz), 7.72 9m, 1H), 6.90 (t, 1H, J= 7.8 Hz), 6.81 (m, 2H), 6.42 (m, 2H), 3.88 (s, 3H), 3.86 (s, 3H); LCMS: purity: 94%; MS (m/e): 358 (MH⁺).

7.3.777 5-Fluoro-N2-(3-hydroxyphenyl)-N4-(5-methylpyridin-2-yl)-2,4-pyrimidinediamine (R927017)

In like manner to the preparation of N4-(3-chloro-4-trifluoromethoxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidineamine, the reaction of 3-hydroxyaniline with 2-chloro-5-fluoro-N4-(5-methylpyridin-2-yl)-4-pyrimidineamine gave 5-fluoro-N2-(3-hydroxyphenyl)-N4-(5-methylpyridin-2-yl)-2,4-pyrimidinediamine. ¹H NMR (DMSO-d₆): δ 11.39 (bs, 1H), 10.59 (bs, 1H), 8.58 (s, 1H), 8.41 (d, 1H, J = 3 Hz), 8.12 (d, 1H, J = 8.7 Hz), 7.82 (d, 1H, J = 8.7 Hz), 7.29 (s, 1H), 7.16 (d, 1H, J = 9 Hz), 7.05 (t, 1H, J = 8.4 Hz), 6.38 (dd, 1H, 1.2 and 6.9 Hz); LCMS: purity: 99%; MS (m/e): 312 (MH⁺).

7.3.778 N4-(6-Chloropyridin-3-yl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine (R927018)

In like manner to the preparation of N4-(3-chloro-4-trifluoromethoxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidineamine, the reaction of 3-hydroxyaniline with 2-chloro-N4-(6-chloropyridin-3-yl)-5-fluoro-4-pyrimidineamine gave N4-(6-chloropyridin-3-yl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine. ¹H NMR (DMSO-d₆): δ 10.10 (bs, 1H), 9.64 (bs, 1H), 8.85 (m, 1H), 8.30 (m, 2H), 8.22 (d, 1H, J = 4.2 Hz), 7.43 (d, 1H, J = 8.7 Hz), 7.01 (m, 3H), 6.42 (bd, 1H, J = 8.4 Hz); LCMS: purity: 93%; MS (m/e): 332 (MH⁺).

7.3.779 5-Fluoro-N2-(3-hydroxyphenyl)-N4-(quinolin-6-yl)-2,4-pyrimidinediamine (R927019)

In like manner to the preparation of N4-(3-chloro-4-trifluoromethoxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidineamine, the reaction of 3-hydroxyaniline with 2-chloro-5-fluoro-N4-(quinolin-6-yl)-4-pyrimidineamine gave 5-fluoro-N2-(3-hydroxyphenyl)-N4-(quinolin-6-yl)-2,4-pyrimidinediamine. ¹H NMR (DMSO-d₆): δ 10.50 (s, 1H), 10.14 (s, 1H), 8.29 (d, 1H, J = 4.8 Hz), 8.14 (d, 1H, J = 1.8 Hz), 7.96 (d, 1H, J = 9.3 Hz), 7.83 (dd, 1H, J = 2.4 and 9.0 Hz), 7.40 (d, 1H, J = 8.7 Hz), 7.04 (t, 1H, J = 8.1 Hz), 6.93 (m, 2H), 6.52 (m, 2H); LCMS: purity: 93%; MS (m/e): 365 (MH⁺).

7.3.780 N4-(5-Chloropyridin-2-yl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine (R927020)

In like manner to the preparation of N4-(3-chloro-4-trifluoromethoxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidineamine, the reaction of 3-hydroxyaniline with 2-chloro-N4-(5-chloropyridin-2-yl)-5-fluoro-4-pyrimidineamine gave N4-(5-chloropyridin-

2-yl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine. ¹H NMR (DMSO-d₆): δ 10.80 (bs, 1H), 9.77 (bs, 1H), 8.45 (bd, 1H), 8.26 (d, 1H, J= 3.9 Hz), 8.15 (d, 1H, J= 8.7 Hz), 7.85 (dd, 1H, J= 2.4 and 8.7 Hz), 7.06 (m, 3H), 6.43 (bd, 1H, J= 7.2 Hz); LCMS: purity: 97%; MS (m/e): 332 (MH⁺).

5 **7.3.781 N4-(4-Chloro-2,5-dimethoxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-primidinediamine (R926860)**

In like manner to the preparation of N4-(3-chloro-4-trifluoromethoxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidineamine, the reaction of 3-hydroxyaniline with 2-chloro-N4-(4-chloro-2,5-dimethoxyphenyl)-5-fluoro-4-pyrimidineamine gave N4-(4-chloro-2,5-dimethoxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-primidinediamine. ¹H NMR (CD₃OD): δ 7.96 (d, 1H, J= 4.8 Hz), 7.66 (s, 1H), 7.13 (s, 1H), 7.07 (t, 1H, J= 8.7 Hz), 8.86 (m, 2H), 6.57 (dd, 1H, J= 3.2 and 8.1 Hz), 3.48 (s, 3H), 3.66 (s, 3H); ¹⁹F NMR (CD₃OD): - 46968.

15 **7.3.782 N4-(4-Chlorophenyl)-5-fluoro-N2-(2-methoxycarbonylbenzofuran-5-yl)-2,4-pyrimidinediamine (R927026)**

In like manner to the preparation of N4-(3-chloro-4-trifluoromethoxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidineamine, the reaction of 5-amino-2-methoxycarbonylbenzofuran with 2-chloro-N4-(4-chlorophenyl)-5-fluoro-4-pyrimidineamine gave N4-(4-chlorophenyl)-5-fluoro-N2-(2-methoxycarbonylbenzofuran-5-yl)-2,4-pyrimidinediamine. ¹H NMR (DMSO-d₆): δ 10.28 (bs, 1H), 10.18 (bs, 1H), 8.25 (d, 1H, J= 4.5 Hz), 7.96 (bs, 1H), 7.84 (m, 1H), 7.67 (m, 3H), 7.57 (m, 1H), 7.37 (bd, 2H, J= 9.0 Hz), 3.88 (s, 3H); LCMS: purity: 96%; MS (m/e): 413 (MH⁺).

25 **7.3.783 N4-(3,4-Dichlorophenyl)-5-fluoro-N2-(2-methoxycarbonylbenzofuran-5-yl)-2,4-pyrimidinediamine (R927027)**

In like manner to the preparation of N4-(3-chloro-4-trifluoromethoxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidineamine, the reaction of 5-amino-2-methoxycarbonylbenzofuran with 2-chloro-N4-(3,4-dichlorophenyl)-5-fluoro-4-pyrimidineamine gave N4-(3,4-dichlorophenyl)-5-fluoro-N2-(2-methoxycarbonylbenzofuran-5-yl)-2,4-pyrimidinediamine. ¹H NMR (DMSO-d₆): δ 9.70

(bs, 1H), 9.50 (bs, 1H), 8.20 (d, 1H, $J=4.5$ Hz), 8.09 (m, 1H), 7.80 (m, 3H), 7.62 (m, 2H), 7.53 (m, 1H), 7.38 (m, 1H), 3.88 (s, 3H); LCMS: purity: 94%; MS (m/e): 448 (MH^+).

7.3.784 5-Fluoro-N4-(3-hydroxyphenyl)-N2-(3-methoxycarbonyl-5-trifluoromethylphenyl)-2,4-pyrimidinediamine (R926863)

5 In like manner to the preparation of N4-(3-chloro-4-trifluoromethoxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidineamine, the reaction of 2-chloro-5-fluoro-N4-(3-hydroxyphenyl)-4-pyrimidineamine with 3-methoxycarbonyl-5-trifluoromethylaniline gave 5-fluoro-N4-(3-hydroxyphenyl)-N2-(3-methoxycarbonyl-5-trifluoromethylphenyl)-2,4-pyrimidinediamine. 1H NMR (DMSO- d_6): δ 9.98 (s, 1H), 9.52 (s, 1H), 8.53 (s, 1H),
10 8.38 (s, 1H), 8.20 (d, 1H, $J=4.2$ Hz), 7.69 (s, 1H), 7.27 (d, 1H, $J=8.1$ Hz), 7.14 (s, 1H), 7.05 (t, 1H, 7.8 Hz), 6.49 (dd, 1H, $J=1.8$ and 8.4 Hz), 3.80 (s, 3H); LCMS: purity: 82%; MS (m/e): 423 (MH^+).

7.3.785 N2-(4-Chloro-2,5-dimethoxyphenyl)-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine (R926857)

15 In like manner to the preparation of N4-(3-chloro-4-trifluoromethoxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidineamine, the reaction of 2-chloro-5-fluoro-N4-(3-hydroxyphenyl)-4-pyrimidineamine with 4-chloro-2,5-dimethoxyaniline gave N2-(4-chloro-2,5-dimethoxyphenyl)-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine. 1H NMR (CD $_3$ OD): δ 8.04 (d, 1H, $J=5.4$ Hz), 7.46 (s, 1H), 7.17 (m, 2H), 7.03 (m, 2H), 6.72
20 (dd, 1H, $J=1.8$ and 7.8 Hz), 3.85 (s, 3H), 3.52 (s, 3H); LCMS: purity: 98%; MS (m/e): 390 (MH^+).

7.3.786 N2-(3-Bromo-5-trifluorophenyl)-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine (R926846)

25 In like manner to the preparation of N4-(3-chloro-4-trifluoromethoxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidineamine, the reaction of 2-chloro-5-fluoro-N4-(3-hydroxyphenyl)-4-pyrimidineamine with 3-bromo-5-trifluoromethylaniline gave N2-(3-bromo-5-trifluorophenyl)-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine. 1H NMR (DMSO- d_6): δ 9.70 (s, 1H), 9.36 (s, 1H), 9.34 (s, 1H), 8.31 (s, 1H), 8.18 (d, 1H, $J=3.6$ Hz), 8.02 (s, 1H), 7.35 (s, 1H), 7.28 (bd, 1H, $J=7.2$ Hz), 7.11 (t, 1H, $J=8.4$ Hz), 7.02
30 (m, 1H), 6.49 (dd, 1H, $J=1.8$ and 7.8 Hz); LCMS: purity: 94%; MS (m/e): 442 (MH^+).

7.3.787 5-Fluoro-N4-(3-hydroxyphenyl)-N2-[3-(1H-pyrazol-3-yl)phenyl]-2,4-pyrimidinediamine (R926841)

In like manner to the preparation of N4-(3-chloro-4-trifluoromethoxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidineamine, the reaction of 2-chloro-5-fluoro-N4-(3-hydroxyphenyl)-4-pyrimidineamine with 3-(1H-pyrazol-3-yl)aniline gave 5-fluoro-N4-(3-hydroxyphenyl)-N2-[3-(1H-pyrazol-3-yl)phenyl]-2,4-pyrimidinediamine. LCMS: purity: 84%; MS 363 (MH⁺)

7.3.788 5-Fluoro-N4-(3-hydroxyphenyl)-N2-[3-(tetrazol-5-yl)phenyl]-2,4-pyrimidinediamine (R926842)

In like manner to the preparation of N4-(3-chloro-4-trifluoromethoxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidineamine, the reaction of 2-chloro-5-fluoro-N4-(3-hydroxyphenyl)-4-pyrimidineamine with 3-(tetrazol-5-yl)aniline gave 5-fluoro-N4-(3-hydroxyphenyl)-N2-[3-(tetrazol-5-yl)phenyl]-2,4-pyrimidinediamine. ¹H NMR (DMSO-d₆): δ 10.05 (bs, 1H), 9.80 (bs, 1H), 8.27 (s, 1H), 8.23 (d, 1H, J= 3.3 Hz), 7.86 (d, 1H, J= 8.1 Hz) 7.65 (d, 1H, J= 6.9 Hz), 7.44 (t, 1H, J= 7.5 Hz), 7.19 (m, 2H), 6.93 (t, 1H, J= 7.5 Hz), 6.49 (dd, 1H, J= 2.4 and 8.1 Hz); LCMS: purity: 89%; MS (m/e): 364 (MH⁺).

7.3.789 5-Fluoro-N4-(3-hydroxyphenyl)-N2-[3-(1,3-oxazol-5-yl)phenyl]-2,4-pyrimidinediamine (R926831)

In like manner to the preparation of N4-(3-chloro-4-trifluoromethoxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidineamine, the reaction of 2-chloro-5-fluoro-N4-(3-hydroxyphenyl)-4-pyrimidineamine with 3-(1,3-oxazol-5-yl)aniline gave 5-fluoro-N4-(3-hydroxyphenyl)-N2-(3-(1,3-oxazol-5-yl)phenyl)-2,4-pyrimidinediamine. LCMS: purity: 76%; MS (m/e): 364 (MH⁺).

7.3.790 N2-(3-Chloro-4-trifluoromethylphenyl)-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinedimine (R926844)

In like manner to the preparation of N4-(3-chloro-4-trifluoromethoxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidineamine, the reaction of 2-chloro-5-fluoro-N4-(3-hydroxyphenyl)-4-pyrimidineamine with 3-chloro-4-trifluoromethoxyaniline gave N2-(3-chloro-4-trifluoromethylphenyl)-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinedimine. ¹H NMR (DMSO-d₆): δ 9.70 (bs, 1H), 9.48 (bs, 1H), 8.15 (bd, 1H, J= 3.6 Hz), 8.06 (s, 1H), 7.62 (dd, 1H, J= 2.4 and 9.3 Hz), 7.37 (d, 1H, J= 9.0 Hz), 7.20 (m, 1H), 7.11 (m, 3H), 6.53 (bd, 1H, J= 8.1 Hz); LCMS: purity: 93%; MS (m/e): 414 (MH⁺).

7.3.791 5-Fluoro-N4-(3,4-ethylenedioxyphenyl)-N2-[3-(tetrazol-5-yl)phenyl]-2,4-pyrimidinediamine (R926843)

In like manner to the preparation of N4-(3-chloro-4-trifluoromethoxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidineamine, the reaction of 2-chloro-5-fluoro-N4-(3,4-ethylenedioxyphenyl)-4-pyrimidineamine with 3-(tetrazol-5-yl)aniline gave 5-fluoro-N4-(3,4-ethylenedioxyphenyl)-N2-[3-(tetrazol-5-yl)phenyl]-2,4-pyrimidinediamine. ¹H NMR (DMSO-d₆): δ 9.91 (s, 1H), 9.74 (s, 1H), 8.29 (s, 1H), 8.18 (d, 1H, J= 4.5 Hz), 7.76 (bdd, 1H, J= 1.5 and 8.1 Hz), 7.64 (d, 1H, J= 8.1 Hz), 7.46 (t, 1H, J= 8.1 Hz), 7.29 (m, 1H), 7.13 (dd, 1H, J= 2.4 and 8.7 Hz), 6.64 (d, 1H, J= 8.7 Hz), 4.11 (m, 4H); LCMS: purity: 91%; MS (m/e): 407 (MH⁺).

7.3.792 N4-(3,4-Ethylenedioxyphenyl)-5-fluoro-N2-(4-methoxy-2-methylphenyl)-2,4-pyrimidinediamine (R926845)

In like manner to the preparation of N4-(3-chloro-4-trifluoromethoxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidineamine, the reaction of 2-chloro-5-fluoro-N4-(3,4-ethylenedioxyphenyl)-4-pyrimidineamine with 4-methoxy-2-methylaniline gave N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(4-methoxy-2-methylphenyl)-2,4-pyrimidinediamine. ¹H NMR (DMSO-d₆): δ 10.30 (bs, 1H), 9.10 (bs, 1H), 8.22 (d, 1H, J= 5.1 Hz), 7.55 (m, 1H), 7.15 (m, 1H), 7.07 (m, 1H), 6.92 (m, 2H), 6.82 (d, 1H, J= 8.7 Hz), 4.22 (bs, 4H), 3.80 (s, 3H), 2.15 (s, 3H); LCMS: purity: 94%; MS (m/e): 383 (MH⁺).

7.3.793 N2-[5-(N-Aminocarbonylmethylene-2-oxo-1,3-oxazol-3(2H)-yl)phenyl]-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R926847)

In like manner to the preparation of N4-(3-chloro-4-trifluoromethoxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidineamine, the reaction of 2-chloro-5-fluoro-N4-(3,4-ethylenedioxyphenyl)-4-pyrimidineamine with 2-[5-amino-2-oxo-1,3-benzoxazol-3(2H)-yl]acetamide gave N2-[5-(N-aminocarbonylmethylene-2-oxo-1,3-oxazol-3(2H)-yl)phenyl]-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine. ¹H NMR (CD₃OD): δ 7.95 (d, 1H, J= 8.4 Hz), 7.32 (dd, 1H, J= 2.4 and 8.1 Hz), 7.24 (d, 1H, J= 2.4 Hz), 7.19 (m, 2H), 6.95 (dd, 1H, J= 2.7 and 9 Hz), 6.80 (d, 1H, J= 9 Hz), 4.51 (s, 2H), 4.21 (m, 4H).

7.3.794 N2-[3-(2-Ethoxycarbonylmethylene-1,3,4-oxadiazol-5-yl)phenyl-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine (R926874)

In like manner to the preparation of N4-(3-chloro-4-trifluoromethoxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidineamine, the reaction of 2-chloro-5-fluoro-N4-(3-hydroxyphenyl)-4-pyrimidineamine with 3-(2-ethoxycarbonylmethylene-1,3,4-oxadiazol-5-yl)aniline gave N2-[3-(2-ethoxycarbonylmethylene-1,3,4-oxadiazol-5-yl)phenyl-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine. ¹H NMR (DMSO-d₆): δ 9.52 (s, 1H), 9.31 (s, 1H), 9.28 (s, 1H), 8.30 (s, 1H), 8.12 (d, 1H, J= 3.6 Hz), 8.00 (m, 1H), 7.49 (d, 1H, J= 7.5 Hz), 7.42 (d, 1H, J= 8.4 Hz), 7.30 (m, 1H), 7.12 (bs, 1H), 7.03 (t, 1H, J= 8.1 Hz), 6.46 (m, 1H), 4.21 (s, 2H), 4.15 (q, 2H, J= 6.9 Hz), 1.19 (t, 3H, J= 7.2 Hz); LCMS: purity: 90%; MS (m/e): 451 (MH⁺).

7.3.795 N2,N4-Bis(3-boronylphenyl)-5-fluoro-2,4-pyrimidinediamine (R926836)

A mixture of 2,4-dichloro-5-fluoro-pyrimidine (1 equivalents) and 3-aminophenylboronic acid (3 equivalents) in MeOH was heated in a sealed tube at 100 °C for 24 hours. The resulting mixture was cooled to room temperature, acidified with 2N HCl and the solid obtained was filtered, washed with water, dried and analyzed to give N2,N4-bis(3-boronylphenyl)-5-fluoro-2,4-pyrimidinediamine. ¹H NMR (DMSO-d₆): δ 10.40 (s, 1H), 10.07 (s, 1H), 8.25 (d, 8.4 Hz), 7.85 (s, 1H), 7.73 (d, 1H, J= 7.5 Hz), 7.63 (bt, 3H), 7.48 (d, 1H, J= 6.9 Hz), 7.30 (t, 1H, J= 8.4 Hz), 7.12 (t, 1H, J= 2.5 Hz); LCMS: purity: 85%; MS (m/e): 368 (MH⁺).

7.3.796 N2-(3-Boronylphenyl)-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R926837)

In like manner to the preparation of N4-(3-chloro-4-trifluoromethoxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidineamine, the reaction of 2-chloro-5-fluoro-N4-(3,4-ethylenedioxyphenyl)-4-pyrimidineamine with 3-aminophenylboronic acid gave N2-(3-boronylphenyl)-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine. LCMS: purity: 99%; MS (m/e): 383 (MH⁺).

7.3.797 (+)-N4-(3,4-Difluorophenyl)-N2-(2,3-dihydro-2-methoxycarbonylbenzofuran-5-yl)-5-fluoro-2,4-pyrimidinediamine (R927030)

A mixture of equivalent amount of 2-chloro-N4-(3,4-difluorophenyl)-5-fluoro-4-pyrimidineamine and (+)-5-amino-2,3-dihydro-2-methoxycarbonylbenzofuran in MeOH was shaken in a sealed tube at 80 °C for 48 h, cooled to room temperature and diluted with a mixture of n-hexanes:EtOAc (1:1; v/v). The resulting solid formed was filtered, washed with a mixture of EtOAc:n-hexanes (1:1; v/v), dried and analyzed to give (+)-N4-(3,4-difluorophenyl)-N2-(2,3-dihydro-2-methoxycarbonylbenzofuran-5-yl)-5-fluoro-2,4-pyrimidinediamine. ¹H NMR (DMSO-d₆): δ 10.21 (bs, 1H), 9.80 (bs, 1H), 8.20 (d, 1H, J= 4.8 Hz), 7.94 (bs, 1H), 7.43 (m, 3H), 7.15 (bd, 1H, J= 8.4 Hz), 6.81 (d, 1H, J= 8.1 Hz), 5.35 (dd, 1H, J= 6.0 and 6.3 Hz), 3.69 (s, 3H), 3.52 (dd, 1H, J= 10.5), 3.22 (dd, 1H, J= 9.0 and 6.0 Hz); LCMS: purity: 99%; MS (m/e): 417 (MH⁺).

7.3.798 (+)-N4-(4-Chlorophenyl)-N2-(2,3-dihydro-2-methoxycarbonylbenzofuran-5-yl)-5-fluoro-2,4-pyrimidinediamine (R927024)

In like manner to the preparation of (+)-N4-(3,4-difluorophenyl)-N2-(2,3-dihydro-2-methoxycarbonylbenzofuran-5-yl)-5-fluoro-2,4-pyrimidinediamine, the reaction of (+)-5-amino-2,3-dihydro-2-methoxycarbonylbenzofuran with 2-chloro-N4-(4-chlorophenyl)-5-fluoro-4-pyrimidineamine gave (+)-N4-(4-chlorophenyl)-N2-(2,3-dihydro-2-methoxycarbonylbenzofuran-5-yl)-5-fluoro-2,4-pyrimidinediamine. ¹H NMR (DMSO-d₆): δ 10.29 (bs, 1H), 9.89 (bs, 1H), 8.21 (d, 1H, J= 4.8 Hz), 7.69 (m, 2H), 7.38 (m, 3H), 7.13 (bd, 1H, J= 8.1 Hz), 6.83 (d, 1H, J= 8.4 Hz), 5.36 (dd, 1H, J= 6.3 and 5.7 Hz), 3.70 (s, 3H), 3.52 (dd, 1H, J= 10.5 Hz), 3.20 (dd, 1H, J= 5.4 and 5.7 Hz); LCMS: purity: 98%; MS (m/e): 415 (MH⁺).

7.3.799 (+)-N4-(3,4-Dichlorophenyl)-N2-(2,3-dihydro-2-methoxycarbonylbenzofuran-5-yl)-5-fluoro-2,4-pyrimidinediamine (R927031)

In like manner to the preparation of (+)-N4-(3,4-difluorophenyl)-N2-(2,3-dihydro-2-methoxycarbonylbenzofuran-5-yl)-5-fluoro-2,4-pyrimidinediamine, the reaction of (+)-5-amino-2,3-dihydro-2-methoxycarbonylbenzofuran with 2-chloro-N4-(3,4-dichlorophenyl)-5-fluoro-4-pyrimidineamine gave (+)-N4-(3,4-dichlorophenyl)-N2-(2,3-dihydro-2-methoxycarbonylbenzofuran-5-yl)-5-fluoro-2,4-pyrimidinediamine. ¹H NMR (DMSO-d₆):

δ 10.13 (bs, 1H), 9.70 (bs, 1H), 8.21 (d, 1H, $J = 4.8$ Hz), 8.04 (d, 1H, $J = 2.4$ Hz), 7.68 (m, 1H), 7.54 (d, 1H, $J = 9.0$ Hz), 7.37 (bs, 1H), 7.19 (m, 1H), 6.80 (d, 1H, $J = 8.7$ Hz), 5.35 (dd, 1H, $J = 6.6$ Hz), 3.69 (s, 3H), 3.53 (dd, 1H, $J = 10.5$ and 11.1 Hz), 3.21 (dd, 1H, $J = 6.0$ Hz); LCMS: purity: 100%; MS (m/e): 450 (MH^+).

5 **7.3.800 (+)-N2-(2,3-Dihydro-2-methoxycarbonylbenzofuran-5-yl)-N4-(2,6-dimethoxypyridin-3-yl)-5-fluoro-2,4-pyrimidinediamine (R927032)**

In like manner to the preparation of (+)-N4-(3,4-difluorophenyl)-N2-(2,3-dihydro-2-methoxycarbonylbenzofuran-5-yl)-5-fluoro-2,4-pyrimidinediamine, the reaction of (+)-5-amino-2,3-dihydro-2-methoxycarbonylbenzofuran with 2-chloro-N4-(2,6-dimethoxypyridin-3-yl)-5-fluoro-4-pyrimidineamine gave (+)-N2-(2,3-dihydro-2-methoxycarbonylbenzofuran-5-yl)-N4-(2,6-dimethoxypyridin-3-yl)-5-fluoro-2,4-pyrimidinediamine. 1H NMR (DMSO- d_6): δ 10.03 (bs, 2H), 8.18 (d, 1H, $J = 4.8$ Hz), 7.68 (bd, 1H, $J = 8.1$ Hz), 7.27 (bs, 1H), 6.98 (bd, 1H, $J = 8.1$ Hz), 6.69 (d, 1H, $J = 8.7$ Hz), 6.44 (d, 1H, $J = 8.1$ Hz), 5.33 (dd, 1H, $J = 5.7$ Hz), 3.88 (s, 3H), 3.86 (s, 3H), 3.69 (s, 3H), 3.42 (dd, 1H, $J = 10.8$ and 11.1 Hz), 3.10 (dd, 1H, $J = 6.3$ and 6.6 Hz); LCMS: purity: 99%; MS (m/e): 442 (MH^+).

20 **7.3.801 (+)-N2-(2,3-Dihydro-2-methoxycarbonylbenzofuran-5-yl)-5-fluoro-N4-[2-(2-hydroxyethyleneoxy)pyridin-5-yl]-5-fluoro-2,4-pyrimidinediamine (R927025)**

In like manner to the preparation of (+)-N4-(3,4-difluorophenyl)-N2-(2,3-dihydro-2-methoxycarbonylbenzofuran-5-yl)-5-fluoro-2,4-pyrimidinediamine, the reaction of (+)-5-amino-2,3-dihydro-2-methoxycarbonylbenzofuran with 2-chloro-5-fluoro-N4-[2-(2-hydroxyethyleneoxy)pyridin-5-yl]-4-pyrimidineamine gave (+)-N2-(2,3-dihydro-2-methoxycarbonylbenzofuran-5-yl)-5-fluoro-N4-[2-(2-hydroxyethyleneoxy)pyridin-5-yl]-2,4-pyrimidinediamine. 1H NMR (DMSO- d_6): δ 10.10 (bs, 1H), 9.70 (bs, 1H), 8.46 (m, 1H), 8.13 (d, 1H, $J = 4.8$ Hz), 7.92 (m, 1H), 7.41 (bs, 1H), 7.12 (bdd, 1H, $J = 8.4$ Hz), 6.79 (m, 2H), 5.35 (dd, 1H, $J = 5.7$ and 6.0 Hz), 4.24 (t, 2H, $J = 5.1$ Hz), 3.70 (s, 3H), 3.69 (t, 2H, $J = 5.1$ Hz), 3.52 (dd, 1H, $J = 11.1$ Hz), 3.24 (dd, 1H, $J = 6.6$ Hz); LCMS: purity: 92%; MS (m/e): 442 (MH^+).

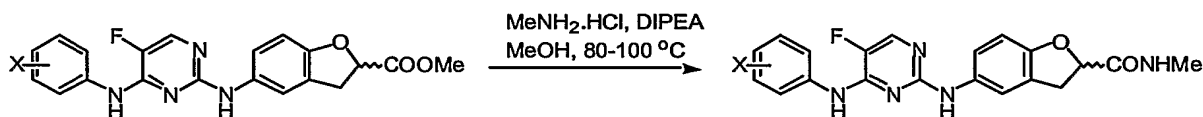
7.3.802 (±)-N2-(2,3-Dihydro-2-methoxycarbonylbenzofuran-5-yl)-5-fluoro-N4-(3-trifluorophenyl)-2,4-pyrimidinediamine (R927028)

In like manner to the preparation of (±)-N4-(3,4-difluorophenyl)-N2-(2,3-dihydro-2-methoxycarbonylbenzofuran-5-yl)-5-fluoro-2,4-pyrimidinediamine, the reaction of (±)-5-amino-2,3-dihydro-2-methoxycarbonylbenzofuran with 2-chloro-5-fluoro-N4-(3-trifluorophenyl)-4-pyrimidineamine gave (±)-N2-(2,3-dihydro-2-methoxycarbonylbenzofuran-5-yl)-5-fluoro-N4-(3-trifluorophenyl)-2,4-pyrimidinediamine. ¹H NMR (DMSO-d₆): δ 10.32 (bs, 1H), 9.90 (bs, 1H), 8.23 (d, 1H, J = 4.8 Hz), 7.80 (bd, 1H, J = 6.9 Hz), 7.73 (bs, 1H), 7.43 (t, 1H, J = 8.1 Hz), 7.36 (bs, 1H), 7.16 (m, 2H), 6.79 (d, 1H, J = 8.1 Hz), 5.33 (dd, 1H, J = 6.0 and 6.6 Hz), 3.69 (s, 3H), 3.51 (dd, 1H, J = 10.5 Hz), 3.20 (dd, 1H, J = 6.0 Hz); LCMS: purity: 98%; MS (m/e): 465 (MH⁺).

7.3.803 (±)-N2-(2,3-Dihydro-2-methoxycarbonylbenzofuran-5-yl)-N4-(3,4-difluoromethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R927029)

In like manner to the preparation of (±)-N4-(3,4-difluorophenyl)-N2-(2,3-dihydro-2-methoxycarbonylbenzofuran-5-yl)-5-fluoro-2,4-pyrimidinediamine, the reaction of (±)-5-amino-2,3-dihydro-2-methoxycarbonylbenzofuran with 2-chloro-N4-(3,4-difluoromethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine gave (±)-N2-(2,3-dihydro-2-methoxycarbonylbenzofuran-5-yl)-N4-(3,4-difluoromethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine. ¹H NMR (DMSO-d₆): δ 10.36 (bs, 1H), 9.93 (bs, 1H), 8.22 (d, 1H, J = 4.8 Hz), 7.91 (bs, 1H), 7.38 (m, 3H), 7.15 (bd, 1H, J = 8.7 Hz), 6.79 (d, 1H, J = 6.0 Hz), 5.33 (dd, 1H, J = 6.3 and 6.6 Hz), 3.69 (s, 3H), 3.50 (dd, 1H, J = 10.5 and 10.8 Hz), 3.22 (dd, 1H, J = 6.0 Hz); LCMS: purity: 100%; MS (m/e): 461 (MH⁺).

Esters were transformed to amides allowing to the scheme illustrated below:



7.3.804 (±)-N4-(3,4-Difluorophenyl)-5-fluoro-N2-[2,3-dihydro-2-(N-methylamino)carbonylbenzofuran-5-yl]-2,4-pyrimidinediamine (R927035)

A mixture of (±)-N4-(3,4-difluorophenyl)-N2-(2,3-dihydro-2-methoxycarbonylbenzofuran-5-yl)-5-fluoro-2,4-pyrimidinediamine, methylamine Hydrogen

Chloride (5 equivalents) and diisopropylethylamine (5 equivalents) in MeOH was shaken in a sealed tube at 80 °C for 24 h. The resulting solution was diluted with water and the precipitate obtained was filtered, washed with water, dried and analyzed to afford (+)-N4-(3,4-difluorophenyl)-5-fluoro-N2-[2,3-dihydro-2-(N-methylamino)carbonylbenzofuran-5-yl]-2,4-pyrimidinediamine. ¹H NMR (DMSO-d₆): δ 9.46 (s, 1H), 9.07 (s, 1H), 8.05 (m, 3H), 7.48 (m, 2H), 7.35 (m, 1H), 7.22 (m, 1H), 6.72 (d, 1H, J= 8.1 Hz), 5.07 (dd, 1H, J= 6.6 and 6.3 Hz), 3.40 (dd, 1H), 3.15 (dd, 1H), 2.60 (d, 3H, J= 4.5 Hz); LCMS: purity: 98%; MS (m/e): 416 (MH⁺).

7.3.805 (+)-N4-(4-Chlorophenyl)-N2-[2,3-dihydro-2-(N-methylamino)carbonylbenzofuran-5-yl]-5-fluoro-2,4-pyrimidinediamine (R927036)

In like manner to the preparation of (+)-N4-(3,4-difluorophenyl)-5-fluoro-N2-[2-(N-methylamino)carbonyl-2,3-dihydrobenzofuran-5-yl]-2,4-pyrimidinediamine, the reaction of methyl amine Hydrogen Chloride with (+)-N4-(4-chlorophenyl)-N2-(2,3-dihydro-2-methoxycarbonylbenzofuran-5-yl)-5-fluoro-2,4-pyrimidinediamine gave (+)-N4-(4-chlorophenyl)-N2-[2,3-dihydro-2-(N-methylamino)carbonylbenzofuran-5-yl]-5-fluoro-2,4-pyrimidinediamine. ¹H NMR (DMSO-d₆): δ 9.40 (s, 1H), 9.02 (s, 1H), 8.05 (m, 2H), 7.84 (dd, 2H, J= 2.7 and 9.3 Hz), 7.51 (bs, 1H), 7.32 (bd, 2H, J= 8.7 Hz), 7.23 (bd, 1H, J= 8.7 Hz), 6.72 (d, 1H, J= 8.7 Hz), 5.07 (dd, 1H, J= 6.0 and 6.3 Hz), 3.39 (dd, 1H), 3.17 (dd, 1H), 2.60 (d, 3H, J= 4.8 Hz); LCMS: purity: 99%; MS (m/e): 414 (MH⁺).

7.3.806 (+)-N4-(3,4-Dichlorophenyl)-N2-[2,3-dihydro-2-(N-methylamino)carbonylbenzofuran-5-yl]-5-fluoro-2,4-pyrimidinediamine (R927037)

In like manner to the preparation of (+)-N4-(3,4-difluorophenyl)-5-fluoro-N2-[2-(N-methylamino)carbonyl-2,3-dihydrobenzofuran-5-yl]-2,4-pyrimidinediamine, the reaction of methyl amine Hydrogen Chloride with (+)-N4-(3,4-dichlorophenyl)-N2-(2,3-dihydro-2-methoxycarbonylbenzofuran-5-yl)-5-fluoro-2,4-pyrimidinediamine gave (+)-N4-(3,4-dichlorophenyl)-N2-[2,3-dihydro-2-(N-methylamino)carbonylbenzofuran-5-yl]-5-fluoro-2,4-pyrimidinediamine. ¹H NMR (DMSO-d₆): δ 9.52 (s, 1H), 9.09 (s, 1H), 8.08 (m, 3H), 7.76 (bd, 1H, J= 9.3 Hz), 7.50 (d, 1H, J= 9.0 Hz), 7.43 (bs, 1H), 7.24 (bd, 1H, J= 8.7 Hz), 6.73 (d, 1H, J= 8.1 Hz), 5.07 (dd, 1H, J= 6.3 and 6.6 Hz), 3.39 (dd, 1H, J= 10.5 Hz), 3.15 (dd, 1H, J= 6.3 Hz), 2.60 (d, 3H, J= 4.8 Hz); LCMS: purity: 99%; MS (m/e): 450 (MH⁺).

7.3.807 (+)-N4-(2,6-Dimethoxypyridin-3-yl)-N2-[2,3-dihydro-2-(N-methylamino)carbonylbenzofuran-5-yl]-5-fluoro-2,4-pyrimidinediamine (R927038)

In like manner to the preparation of (+)-N4-(3,4-difluorophenyl)-5-fluoro-N2-[2-(N-methylamino)carbonyl-2,3-dihydrobenzofuran-5-yl]-2,4-pyrimidinediamine, the reaction of methyl amine Hydrogen Chloride with (+)-N4-(2,6-dimethoxypyridin-3-yl)-N2-(2,3-dihydro-2-methoxycarbonylbenzofuran-5-yl)-5-fluoro-2,4-pyrimidinediamine gave (+)-N4-(2,6-dimethoxypyridin-3-yl)-N2-[2,3-dihydro-2-(N-methylamino)carbonylbenzofuran-5-yl]-5-fluoro-2,4-pyrimidinediamine. ¹H NMR (CD₃OD): δ 7.98 (d, 1H, J= 8.1 Hz), 7.81 (d, 1H, J= 3.6 Hz), 7.39 (bd, 1H, J= 2.4 Hz), 7.06 (dd, 1H, J= 2.4 and 8.7 Hz), 6.72 (d, 1H, J= 8.1 Hz), 6.31 (d, 1H, J= 8.7 Hz), 5.07 (dd, 1H, J= 6.3 Hz), 3.96 (s, 3H), 3.93 (s, 3H), 3.46 (dd, 1H, J= 7.8 and 10.5 Hz), 3.19 (dd, 1H, J= 5.7 and 6.3 Hz), 2.77 (d, 3H, J= 4.8 Hz); LCMS: purity: 98%; MS (m/e): 441 (MH⁺).

7.3.808 (+)-N2-[2,3-Dihydro-(N-methylamino)carbonylbenzofuran-5-yl]-5-fluoro-N4-[2-(2-hydroxyethyleneoxy)pyridin-5-yl]-2,4-pyrimidinediamine (R927039)

In like manner to the preparation of (+)-N4-(3,4-difluorophenyl)-5-fluoro-N2-[2-(N-methylamino)carbonyl-2,3-dihydrobenzofuran-5-yl]-2,4-pyrimidinediamine, the reaction of methyl amine Hydrogen Chloride with (+)-N2-(2,3-dihydro-2-methoxycarbonylbenzofuran-5-yl)-5-fluoro-N4-[2-(2-hydroxyethyleneoxy)pyridin-5-yl]-2,4-pyrimidinediamine gave (+)-5-fluoro-N4-[2-(2-hydroxyethyleneoxy)pyridin-5-yl]-N2-[2-(N-methylamino)carbonyl-2,3-dihydrobenzofuran-5-yl]-2,4-pyrimidinediamine. ¹H NMR (DMSO-d₆): δ 9.26 (s, 1H), 8.99 (s, 1H), 8.50 (bd, 1H, J= 3.0 Hz), 8.02 (bd, 2H, J= 3.6 Hz), 7.94 (dd, 2H, J= 2.7 and 5.1 Hz), 7.52 (bs, 1H), 7.20 (bd, 1H, J= 8.7 Hz), 6.78 (d, 1H, J= 8.7 Hz), 6.67 (d, 1H, J= 8.7 Hz), 5.05 (dd, 1H, J= 6.3 and 6.6 Hz), 4.80 (t, 1H), 4.23 (t, 2H, J= 5.1 Hz), 3.69 (q, 2H, J= 5.4 Hz), 3.40 (dd, 1H), 3.15 (dd, 1H, J= 6.3 and 9.9 Hz), 2.60 (d, 3H, J= 4.5 Hz); LCMS: purity: 86%; MS (m/e): 441 (MH⁺).

7.3.809 (+)-N2-[2,3-Dihydro-(N-methylamino)carbonylbenzofuran-5-yl]-5-fluoro-N4-(3-trifluoromethoxyphenyl)-2,4-pyrimidinediamine (R927040)

In like manner to the preparation of (+)-N4-(3,4-difluorophenyl)-5-fluoro-N2-[2-(N-methylamino)carbonyl-2,3-dihydrobenzofuran-5-yl]-2,4-pyrimidinediamine, the reaction of methyl amine Hydrogen Chloride with (+)-N2-(2,3-dihydro-2-methoxycarbonylbenzofuran-5-yl)-5-fluoro-N4-(3-trifluoromethoxyphenyl)-2,4-pyrimidinediamine gave (+)-N2-[2,3-

dihydro-(N-methylamino)carbonylbenzofuran-5-yl]-5-fluoro-N4-(3-trifluoromethoxyphenyl)-2,4-pyrimidinediamine. LCMS: purity: 94%; MS (m/e): 464 (MH⁺).

5 **7.3.810 (±)-N2-[2,3-Dihydro-(N-methylamino)carbonylbenzofuran-5-yl]-N4-(3,4-difluoromethyleneoxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R927041)**

In like manner to the preparation of (±)-N4-(3,4-difluorophenyl)-5-fluoro-N2-[2-(N-methylamino)carbonyl-2,3-dihydrobenzofuran-5-yl]-2,4-pyrimidinediamine, the reaction of methyl amine Hydrogen Chloride with (±)-N2-(2,3-dihydro-2-methoxycarbonylbenzofuran-5-yl)-5-fluoro-N4-(3-trifluoromethoxyphenyl)-2,4-pyrimidinediamine gave (±)-N2-[2,3-dihydro-(N-methylamino)carbonylbenzofuran-5-yl]-N4-(3,4-difluoromethyleneoxyphenyl)-5-fluoro-2,4-pyrimidinediamine. ¹H NMR (DMSO-d₆): δ 9.46 (s, 1H), 9.05 (s, 1H), 8.05 (m, 3H), 7.43 (m, 2H), 7.31 (d, 1H, J= 8.7 Hz), 7.23 (bd, 1H, J= 7.5 Hz), 6.70 (d, 1H, J= 9.0 Hz), 5.04 (dd, 1H, J= 6.6 Hz), 3.40 (dd, 1H), 3.14 (dd, 1H, J= 5.7 and 6.6 Hz), 2.60 (d, 3H, J= 3.9 Hz); LCMS: purity: 94%; MS (m/e): 460 (MH⁺).

7.3.811 N2-(4-Carboxymethyleneoxyphenyl)-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R926238)

The reaction of N2-(4-ethoxycarbonylmethyleneoxyphenyl)-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine with LiOH in THF:H₂O at room temperature gave N2-(carboxymethyleneoxyphenyl)-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine. ¹H NMR (DMSO-d₆): δ 8.16 (d, 1H, J= 4.8 Hz), 7.37 (bd, 2H, J= 9 Hz), 7.25 (d, 1H, J= 3 Hz), 7.08 (m, 1H), 6.83 (m, 3H), 4.64 (s, 2H), 4.23 (s, 4H); LCMS: ret. time: 19.15 min.; purity: 100%; MS (m/e): 413 (MH⁺).

25 **7.3.812 N4-(1,4-Benzoxazin-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine Hydrogen Chloride Salt (R920395)**

To a solution of N4-(1,4-benzoxazin-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (1 equivalent) in MeOH at 0 °C was added HCl (4M, dioxane, 1.1 equivalents) dropwise and shaken for 5 minutes. The resulting solution was diluted with EtOAc and the solid obtained was filtered washed with EtOAc, dried and analyzed to give N4-(1,4-benzoxazin-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine Hydrogen Chloride

Salt. ¹H NMR (DMSO-d₆): δ 9.80 (bs, 2H), 8.12 (d, 1H, J= 4.8 Hz), 7.89 (bd, 1H, J= 4.5 Hz), 7.18 (m, 3H), 8.24 (m, 2H), 6.60 (bd, 2H, J= 8.1 Hz), 4.36 (s, 2H), 4.10 (t, 2H, J= 3.9 Hz), 3.27 (t, 2H, J= 3.9 Hz), 2.62 (d, 3H, J= 4.5 Hz); LCMS: purity: 98%, MS (m/e): 425 (MH⁺).

5 **7.3.813 N4-(3,4-Ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine Trifluoro Acetic Acid Salt (R926826)**

In like manner to the synthesis of N4-(1,4-benzoxazin-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine Hydrogen Chloride
10 Salt the reaction of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine with trifluoroacetic acid gave N4-(3,4-Ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine Trifluoro Acetic Acid
15 Salt. ¹H NMR (DMSO-d₆): δ 9.40 (bs, 1H), 9.36 (bs, 1H), 8.07 (d, 1H, J= 4.2 Hz), 7.94 (bd, 1H), 7.22 (m, 4H), 7.11 (t, 1H, J= 7.5 Hz), 6.79 (d, 1H, J= 8.7 Hz), 6.51 (bd, 1H, J= 7.5 Hz), 4.33 (s, 2H), 4.21 (bs, 4H), 2.63 (d, 3H, 3.3 Hz).

20 **7.3.814 5-Fluoro-N4-[(1H)-indol-6-yl]-N2-[4-methoxy-3-[(N-methylamino)carbonylmethyleneoxy]phenyl]-2,4-pyrimidinediamine (R926752)**

In a like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro -N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-[(1H)indol-6-yl]-4-pyrimidineamine and 4-methoxy-3-[(N-methylamino)carbonylmethyleneoxy]aniline were reacted to produce 5-fluoro-N4-[(1H)-indol-6-yl]-N2-[4-methoxy-3-[(N-methylamino)carbonylmethyleneoxy]phenyl]-2,4-pyrimidinediamine. ¹H NMR (CD₃OD): δ
25 7.83 (d, 1H, J= 3.6 Hz), 7.73 (d, 1H, J= 0.9 Hz), 7.49 (d, 1H, J= 8.1 Hz), 7.39 (d, 1H, J= 3.0 Hz), 7.20 (d, 1H, J= 3.6 Hz), 7.15 (dd, 1H, J= 1.8 and 8.1 Hz), 7.05 (dd, 1H, J= 2.1 and 8.7 Hz), 6.81 (d, 1H, J= 8.7 Hz), 6.41 (d, 1H, J= 4.2 Hz), 4.09 (s, 2H), 3.81 (s, 3H), 2.76 (s, 3H); LCMS: purity: 100%; MS (m/e): 437(MH⁺).

7.3.815 5-Fluoro-N4-(3-hydroxy-4-methylphenyl)-N2-[3-[(N-methylamino)carbonylmethyleneoxy]phenyl]-2,4-pyrimidinediamine (R926753)

In a like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro -N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-(2-hydroxy-4-methylphenyl)-4-pyrimidineamine and 3-[(N-methylamino)carbonylmethyleneoxy] aniline were reacted to produce 5-fluoro-N4-(3-hydroxy-4-methylphenyl)-N2-[3-[(N-methylamino)carbonylmethyleneoxy]phenyl]-2,4-pyrimidinediamine. ¹H NMR (DMSO-*d*₆): δ 9.95 (bs, 1H), 9.83 (bs, 1H), 9.38 (bs, 1H), 8.17 (d, 1H, J= 4.4 Hz), 7.97 (d, 1H, J= 4.8 Hz), 7.24-7.17 (m, 2H), 7.16 (d, 1H, J= 8.4 Hz), 7.10 (dd, 1H, J=1.8 and 8.4 Hz), 7.03 (d, 1H, J= 2.4 Hz), 7.00 (d, 1H, J= 9.0 Hz), 6.61 (d, 1H, J= 8.7 Hz), 4.34 (s, 2H), 2.63 (d, 3H, J= 4.5 Hz), 2.08 (s, 3H); LCMS: purity: 96%; MS (m/e): 398(MH⁺).

7.3.816 5-Fluoro-N4-(3-dihydroxyborylphenyl)- N2-[3-[(N-methylamino)carbonylmethyleneoxy]phenyl]-2,4-pyrimidinediamine (R926754)

In a like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro -N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-(3-dihydroxyborylphenyl)-4-pyrimidineamine and 3-[(N-methylamino)carbonylmethyleneoxy]aniline were reacted to produce 5-fluoro-N4-(3-dihydroxyborylphenyl)- N2-[3-[(N-methylamino)carbonylmethyleneoxy]phenyl]-2,4-pyrimidinediamine. ¹H NMR (DMSO-*d*₆): δ 9.38 (bs, 1H), 9.22 (bs, 1H), 8.08 (d, 1H, J= 3.6 Hz), 8.06-7.81 (m, 4H), 7.51 (d, 1H, J= 8.1 Hz), 7.33-7.28 (m, 3H), 7.06 (t, 1H, J= 8.1 Hz), 6.44 (dd, 1H, J= 2.4 and 7.5 Hz), 4.33 (s, 2H), 2.63 (d, 3H, J= 4.8 Hz); LCMS: purity: 95%; MS (m/e): 412(MH⁺).

7.3.817 5-Fluoro-N4-(3-dihydroxyborylphenyl)-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine (R926755)

In a like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro -N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-(3-dihydroxyborylphenyl)-4-pyrimidineamine and 3-hydroxyaniline were reacted to produce 5-Fluoro-N4-(3-dihydroxyborylphenyl)-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine. ¹H NMR (DMSO-*d*₆): δ 9.68 (bs, 1H), 9.35 (bs, 1H), 9.22 (bs, 1H), 8.10 (d, 1H, J= 3.9 Hz), 7.88-7.80 (m, 2H), 7.54 (d, 1H, J= 7.2 Hz), 7.31 (t, 1H, J= 7.2 Hz), 7.08 (d, 1H, J= 8.4 Hz), 6.98-6.93 (m, 2H), 6.35 (d, 1H, J= 8.4 Hz); LCMS: purity: 96%; MS (m/e): 341(MH⁺).

7.3.818 N2-(3,4-Ethylenedioxyphenyl)-5-fluoro-N4-(3-hydroxyborylphenyl)-2,4-pyrimidinediamine (R926756)

In a like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro -N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-(3-dihydroxyborylphenyl)-4-pyrimidineamine and 3,4-ethylenedioxyaniline were reacted to produce N2-(3,4-ethylenedioxyphenyl)-5-fluoro-N4-(3-hydroxyborylphenyl)-2,4-pyrimidinediamine. ¹H NMR (DMSO-*d*₆): δ 9.46 (bs, 1H), 9.11 (bs, 1H), 8.05 (d, 1H, J= 4.2 Hz), 7.95 (bs, 1H), 7.88 (s, 1H), 7.78 (d, 1H, J= 7.5 Hz), 7.52 (d, 1H, J= 7.5 Hz), 7.29 (t, 1H, J= 7.5 Hz), 7.16 (s, 1H), 7.02 (d, 1H, J= 8.7 Hz), 6.65 (d, 1H, J= 8.7 Hz), 3.40 (s, 4H); LCMS: purity: 98%; MS (m/e): 383(MH⁺).

7.3.819 5-Fluoro-N4-(3-hydroxyphenyl)-N2-[4-methyl-3-[(N-methylamino)carbonylmethyleneoxy]phenyl]-2,4-pyrimidinediamine (R926757)

In a like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro -N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-(3-hydroxyphenyl)-4-pyrimidineamine and 4-methyl-3-[(N-methylamino)carbonylmethyleneoxy]aniline were reacted to produce 5-fluoro-N4-(3-hydroxyphenyl)-N2-[4-methyl-3-[(N-methylamino)carbonylmethyleneoxy]phenyl]-2,4-pyrimidinediamine. ¹H NMR (DMSO-*d*₆): δ 9.32 (s, 1H), 9.17 (s, 1H), 9.04 (s, 1H), 8.04 (d, 1H, J= 4.2 Hz), 7.76 (d, 1H, J= 4.8 Hz), 7.32 (td, 2H, J= 1.8 and 8.1 Hz), 7.13-7.04 (m, 3H), 6.95 (d, 1H, J= 8.4 Hz), 6.46 (dd, 1H, J= 1.8 and 8.4 Hz), 4.31 (s, 2H), 2.65 (d, 3H, J= 4.8 Hz), 2.14 (s, 3H); LCMS: purity: 99%; MS (m/e): 398(MH⁺).

7.3.820 N4-(3,4-Ethylenedioxyphenyl)-5-fluoro- N2-[4-methyl-3-[(N-methylamino)carbonylmethyleneoxy]phenyl]-2,4-pyrimidinediamine (R926758)

In a like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro -N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine and 4-methyl-3-[(N-methylamino)carbonylmethyleneoxy]aniline were reacted to produce N4-(3,4-ethylenedioxyphenyl)-5-fluoro- N2-[4-methyl-3-[(N-methylamino)carbonylmethyleneoxy]phenyl]-2,4-pyrimidinediamine. ¹H NMR (DMSO-*d*₆): δ 9.13 (bs, 1H), 9.05 (s, 1H), 8.01 (d, 1H, J= 4.2 Hz), 7.76 (d, 1H, J= 4.8 Hz), 7.32 (d, 1H, J= 2.4 Hz), 7.27 (dd, 1H, J= 2.4 and 8.1 Hz), 7.21 (dd, 1H, J= 2.4 and 8.7 Hz), 7.13 (d,

1H, J= 1.8 Hz), 6.95 (d, 1H, J= 8.1 Hz), 6.76 (d, 1H, J= 8.7 Hz), 4.28 (s, 2H), 4.20 (s, 4H), 2.65 (d, 3H, J= 4.8 Hz), 2.15 (s, 3H); LCMS: purity: 97%; MS (m/e): 440(MH⁺).

7.3.821 5-Fluoro-N4-(3-hydroxy-4-methylphenyl)-N2-[4-methyl-3-[(N-methylamino)carbonylmethyleneoxy]phenyl]-2,4-pyrimidinediamine (R926759)

In a like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro -N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-(2-hydroxy-4-methylphenyl)-4-pyrimidineamine and 4-methyl-3-[(N-methylamino)carbonylmethyleneoxy]aniline were reacted to produce 5-fluoro-N4-(3-hydroxy-4-methylphenyl)-N2-[4-methyl-3-[(N-methylamino)carbonylmethyleneoxy]phenyl]-2,4-pyrimidinediamine. ¹H NMR (DMSO-*d*₆): δ 10.09 (bs, 1H), 9.96 (bs, 1H), 9.44 (bs, 1H), 8.16 (d, 1H, J= 4.8 Hz), 7.81 (d, 1H, J= 4.8 Hz), 7.13-6.94 (m, 6H), 4.29 (s, 2H), 2.64 (d, 3H, J= 4.5 Hz), 2.17 (s, 3H), 2.07 (s, 3H); LCMS: purity: 99%; MS (m/e): 412(MH⁺).

7.3.822 5-Fluoro-N2,N4-bis[4-methyl-3-[(N-methylamino)carbonylmethyleneoxy]phenyl]-2,4-pyrimidinediamine (R926760)

In a like manner to the preparation of N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, 2,4-dichloro-5-fluoropyrimidine and 4-methyl-3-[(N-methylamino)carbonylmethyleneoxy]aniline were reacted to provide 5-fluoro-N2,N4-bis[4-methyl-3-[(N-methylamino)carbonylmethyleneoxy]phenyl]-2,4-pyrimidinediamine. ¹H NMR (DMSO-*d*₆): δ 9.30 (s, 1H), 9.02 (s, 1H), 8.06 (d, 1H, J= 3.6 Hz), 7.94 (d, 1H, J= 4.5 Hz), 7.80 (d, 1H, J= 4.2 Hz), 7.58 (bs, 1H), 7.31-7.22 (m, 3H), 7.05 (d, 1H, J= 9.0 Hz), 6.97 (d, 1H, J= 7.5 Hz), 4.41 (s, 2H), 4.27 (s, 2H), 2.66 (d, 3H, J= 4.2 Hz), 2.63 (d, 3H, J= 4.2 Hz), 2.18 (s, 3H), 2.14 (s, 3H); LCMS: purity: 100%; MS (m/e): 483(MH⁺).

7.3.823 5-Fluoro-N4-(3-hydroxyphenyl)-N2-(3,4,5-trimethoxyphenyl)-2,4-pyrimidinediamine (R926761)

In a like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro -N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-(3-hydroxyphenyl)-4-pyrimidineamine and 3,4,5-trimethoxyaniline were reacted to produce 5-fluoro-N4-(3-hydroxyphenyl)-N2-(3,4,5-trimethoxyphenyl)-2,4-pyrimidinediamine. ¹H NMR (DMSO-*d*₆): δ 9.33 (s, 1H), 9.17 (s, 1H), 8.99 (s, 1H), 8.06 (d, 1H, J= 3.3 Hz), 7.27 (d, 1H, J= 7.5

Hz), 7.08-7.02 (m, 4H), 6.46 (dd, 1H, J= 1.8 and 7.8 Hz), 3.60 (s, 6H), 3.57 (s, 3H); LCMS: purity: 99%; MS (m/e): 387(MH⁺).

7.3.824 N4-(3,4-Ethylenedioxyphenyl)-5-fluoro-N2-(3,4,5-trimethoxyphenyl)-2,4-pyrimidinediamine (R926762)

5 In a like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro -N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine and 3,4,5-trimethoxyaniline were reacted to produce N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3,4,5-trimethoxyphenyl)-2,4-pyrimidinediamine
1H NMR (DMSO-d₆): δ 8.08 (d, 1H, J= 4.8 Hz), 7.29 (d, 1H, J= 2.4 Hz), 7.15 (dd, 1H,
10 J=3.0 and 9.0 Hz), 6.91 (s, 1H), 6.76 (d, 1H, J= 8.7 Hz), 4.20 (s, 4H), 3.61 (s, 6H), 3.59 (s, 3H); LCMS: purity: 97%; MS (m/e): 429(MH⁺).

7.3.825 N4-(3,4-Ethylenedioxyphenyl)-5-fluoro-N2-(3,5-dichloro-4-hydroxyphenyl)-2,4-pyrimidinediamine (R926763)

In a like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro -N2-
15 (3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine and 3,5-dichloro-4-hydroxyaniline were reacted to produce N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3,5-dichloro-4-hydroxyphenyl)-2,4-pyrimidinediamine. 1H NMR (DMSO-d₆): δ 9.50 (bs, 1H), 9.26 (bd, 2H, J= 7.5 Hz), 8.06 (d, 1H, J= 3.9 Hz), 7.65 (s, 2H), 7.18-7.13 (m, 2H), 6.80 (d, 1H, J= 9.0 Hz), 4.20 (s, 4H);
20 LCMS: purity: 100%; MS (m/e): 424(MH⁺).

7.3.826 5-Fluoro-N2-(3,5-dichloro-4-hydroxyphenyl)-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine (R926890)

In a like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro -N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-(3-hydroxyphenyl)-4-
25 pyrimidineamine and 3,5-dichloro-4-hydroxyaniline were reacted to produce 5-Fluoro-N2-(3,5-dichloro-4-hydroxyphenyl)-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine. 1H NMR (DMSO-d₆): δ 9.47 (bs, 1H), 9.35 (bs, 1H), 9.22 (bs, 2H), 8.09 (d, 1H, J= 3.6 Hz), 7.70 (s, 2H), 7.31 (dd, 1H, J= 1.2 and 9.3 Hz), 7.10 (t, 1H, J= 7.5 Hz), 7.00 (bs, 1H), 6.48 (dd, 1H, J= 1.2 and 6.9 Hz); LCMS: purity: 93%; MS (m/e): 382(MH⁺).

7.3.827 N4-(3-Chloro-4-methoxyphenyl)-5-fluoro-N2-[3-[(N-methylamino)carbonylmethyleneoxy]phenyl]-2,4-pyrimidinediamine (R926891)

In a like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro -N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N4-(3-chloro-4-methoxyphenyl)-5-fluoro-4-pyrimidineamine and 3-[(N-methylamino)carbonylmethyleneoxy]aniline were reacted to produce N4-(3-chloro-4-methoxyphenyl)-5-fluoro-N2-[3-[(N-methylamino)carbonylmethyleneoxy]phenyl]-2,4-pyrimidinediamine. ¹H NMR (DMSO-*d*₆): δ 9.85 (bs, 1H), 9.70 (bs, 1H), 8.17 (d, 1H, J= 4.8 Hz), 7.98 (d, 1H, J= 3.9 Hz), 7.79 (d, 1H, J= 2.4 Hz), 7.65 (dd, 1H, J= 3.0 and 9.3 Hz), 7.24-7.09 (m, 4H), 6.57 (d, 1H, J= 5.7 Hz), 4.34 (s, 2H), 3.82 (s, 3H), 2.62 (d, 3H, J= 4.8 Hz); LCMS: purity: 95%; MS (m/e): 433(MH⁺).

7.3.828 5-Fluoro-N4-(3-fluoro-4-methoxyphenyl)-N2-[3-[(N-methylamino)carbonylmethyleneoxy]phenyl]-2,4-pyrimidinediamine (R926892)

In a like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro -N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-(3-fluoro-4-methoxyphenyl)-4-pyrimidineamine and 3-[(N-methylamino)carbonylmethyleneoxy]aniline were reacted to produce 5-fluoro-N4-(3-fluoro-4-methoxyphenyl)-N2-[3-[(N-methylamino)carbonylmethyleneoxy]phenyl]-2,4-pyrimidinediamine. ¹H NMR (DMSO-*d*₆): δ 9.68 (bs, 1H), 9.53 (bs, 1H), 8.13 (d, 1H, J= 4.2 Hz), 7.97 (d, 1H, J= 4.8 Hz), 7.76 (dd, 1H, J= 2.4 and 13.5 Hz), 7.47 (d, 1H, J= 7.5 Hz), 7.27-7.08 (m, 4H), 6.54 (d, 1H, J= 8.4 Hz), 4.35 (s, 2H), 3.80 (s, 3H), 2.63 (d, 3H, J= 4.8 Hz); LCMS: purity: 94%; MS (m/e): 416(MH⁺).

7.3.829 N4-(3,4-Ethylenedioxyphenyl)-5-fluoro-N4-(3-hydroxy-5-methylphenyl)-2,4-pyrimidinediamine (R926893)

In like manner to the preparation of 5-fluoro-N4-(3-hydroxyphenyl)-N2-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine, 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine, 4-amino-*m*-cresol hydrogenschloride salt, and diisopropylethylamine were reacted to provide N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N4-(3-hydroxy-5-methylphenyl)-2,4-pyrimidinediamine.

¹H NMR (DMSO-*d*₆): δ 9.06 (s, 1H), 8.94 (s, 1H), 8.11 (s, 1H), 7.86 (d, 1H, J= 3.9 Hz), 7.21-7.15 (m, 2H), 7.03 (d, 1H, J= 8.1 Hz), 6.59 (bd, 2H, J= 8.7 Hz), 6.52 (dd, 1H, J= 3.0 and 8.1 Hz), 4.17 (s, 4H), 2.05 (s, 3H); LCMS: purity: 99%; MS (m/e): 369(MH⁺).

7.3.830 N4-(3,4-Ethylenedioxyphenyl)-5-fluoro-N2-(3-fluoro-5-trifluoromethylphenyl)-2,4-pyrimidinediamine (R926894)

In like manner to the preparation of 5-fluoro-N4-(3-hydroxyphenyl)-N2-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine, 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine and 3-amino-5-fluorobenzotrifluoride were reacted to provide N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-fluoro-5-trifluoromethylphenyl)-2,4-pyrimidinediamine. ¹H NMR (DMSO-*d*₆): δ 9.75 (s, 1H), 9.32 (d, 1H, J= 1.2 Hz), 8.13 (d, 1H, J= 3.6 Hz), 7.99 (d, 1H, J= 12.3 Hz), 7.77 (s, 1H), 7.21 (d, 1H, J= 2.4 Hz), 7.13 (dd, 1H, J= 2.1 and 8.7 Hz), 7.03 (d, 1H, J= 9.0 Hz), 6.80 (d, 1H, J= 8.7 Hz), 4.21 (s, 4H); LCMS: purity: 97%; MS (m/e): 425(MH⁺).

7.3.831 N4-(3,4-Ethylenedioxyphenyl)-5-fluoro-N2-(3-methyl-5-trifluoromethylphenyl)-2,4-pyrimidinediamine (R926895)

In like manner to the preparation of 5-fluoro-N4-(3-hydroxyphenyl)-N2-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine, 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine and 3-amino-5-methylbenzotrifluoride were reacted to provide N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-methyl-5-trifluoromethylphenyl)-2,4-pyrimidinediamine. ¹H NMR (DMSO-*d*₆): δ 9.57 (bs, 1H), 9.39 (bs, 1H), 8.12 (d, 1H, J= 3.6 Hz), 7.77 (s, 2H), 7.25-7.13 (m, 2H), 7.02 (s, 1H), 6.79 (d, 1H, J= 9.0 Hz), 4.20 (s, 4H), 2.27 (s, 3H); LCMS: purity: 100%; MS (m/e): 421(MH⁺).

7.3.832 N4-(3,4-Ethylenedioxyphenyl)-5-fluoro-N2-(5-methoxy-2-methylphenyl)-2,4-pyrimidinediamine (R926896)

In like manner to the preparation of 5-fluoro-N4-(3-hydroxyphenyl)-N2-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine, 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine and 5-methoxy-2-methylaniline were reacted to provide N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(5-methoxy-2-methylphenyl)-2,4-pyrimidinediamine. ¹H NMR (CDCl₃): δ 7.91 (bs, 1H), 7.61 (d, 1H, J= 2.1 Hz), 7.17 (d, 1H, J= 3.0 Hz), 7.05 (d, 1H, J= 9.3 Hz), 7.03 (dd, 1H, J= 3.0 and 8.7 Hz),

6.82 (d, 1H, J= 8.1 Hz), 6.68-6.60 (m, 2H), 6.55 (dd, 1H, J= 2.1 and 8.1 Hz), 4.26 (s, 4H), 3.70 (s, 3H), 2.22 (s, 3H); ^{19}F NMR (282 MHz, CDCl_3): -47450; LCMS: purity: 99%; MS (m/e): 383(MH^+).

5 **7.3.833 N4-(3,4-Ethylenedioxyphenyl)-5-fluoro-N2-(2-fluoro-5-methylphenyl)-2,4-pyrimidinediamine (R926897)**

In like manner to the preparation of 5-fluoro-N4-(3-hydroxyphenyl)-N2-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine, 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine and 2-fluoro-5-methylaniline were reacted to provide N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(2-fluoro-5-methylphenyl)-
10 2,4-pyrimidinediamine. ^1H NMR (CDCl_3): δ 8.11 (dd, 1H, J= 1.8 and 8.1 Hz), 7.94 (d, 1H, J= 2.7 Hz), 7.08-6.84 (m, 4H), 6.74-6.67 (m, 1H), 6.64-6.59 (m, 1H), 4.27 (s, 4H), 2.28 (s, 3H); ^{19}F NMR (282 MHz, CDCl_3): -38659, -47267; LCMS: purity: 100%; MS (m/e): 371(MH^+).

15 **7.3.834 N4-(3,4-Ethylenedioxyphenyl)-5-fluoro-N2-(3,5-difluorophenyl)-2,4-pyrimidinediamine (R926898)**

In like manner to the preparation of 5-fluoro-N4-(3-hydroxyphenyl)-N2-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine, 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine and 3,5-difluoroaniline were reacted to provide N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3,5-difluorophenyl)-2,4-
20 pyrimidinediamine. ^1H NMR (CDCl_3): δ 7.94 (d, 1H, J= 3.3 Hz), 7.20-7.11 (m, 3H), 7.02 (s, 1H), 6.92-6.90 (m, 2H), 6.65 (s, 1H), 6.39 (tt, 1H, J= 2.4 and 9.0 Hz), 4.31 (s, 4H); ^{19}F NMR (282 MHz, CDCl_3): -31142, -47002; LCMS: purity: 97%; MS (m/e): 375(MH^+).

25 **7.3.835 N4-(3,4-Ethylenedioxyphenyl)-5-fluoro-N2-(4-trifluoromethylthiophenyl)-2,4-pyrimidinediamine (R926899)**

In like manner to the preparation of 5-fluoro-N4-(3-hydroxyphenyl)-N2-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine, 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine and 4-(trifluoromethylthio)aniline were reacted to provide N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(4-
30 trifluoromethylthiophenyl)-2,4-pyrimidinediamine. ^1H NMR ($\text{DMSO}-d_6$): δ 9.73 (s, 1H), 9.47 (s, 1H), 8.13 (d, 1H, J= 3.6 Hz), 7.79 (d, 2H, J= 9.0 Hz), 7.51 (d, 2H, J= 9.0 Hz), 7.28

(d, 1H, J= 2.1 Hz), 7.12 (dd, 1H, J= 2.4 and 9.0 Hz), 6.83 (d, 1H, J= 8.7 Hz), 4.23 (s, 4H);
¹⁹F NMR (282 MHz DMSO-*d*₆): -12306; LCMS: purity: 97%; MS (m/e): 439(MH⁺).

7.3.836 N4-[3-(Benzothiazol-2-yl)-4-chlorophenyl]-5-fluoro-N2-[3-[(N-methylamino)carbonylmethyleneoxy]phenyl]-2,4-pyrimidinediamine (R926900)

In like manner to the preparation of 5-fluoro-N4-(3-hydroxyphenyl)-N2-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine, N4-[3-(Benzothiazol-2-yl)-4-chlorophenyl]-2-chloro-5-fluoro-4-pyrimidineamine and 3-[(N-methylamino)carbonylmethyleneoxy]aniline were reacted to provide N4-[3-(benzothiazol-2-yl)-4-chlorophenyl]-5-fluoro-N2-[3-[(N-methylamino)carbonylmethyleneoxy]phenyl]-2,4-pyrimidinediamine. ¹H NMR (DMSO-*d*₆): δ 9.77 (s, 1H), 9.30 (s, 1H), 8.49 (d, 1H, J= 3.0 Hz), 8.25 (dd, 1H, J= 3.0 and 9.0), 8.21-8.16 (m, 2H), 8.06 (d, 1H, J= 7.8 Hz), 7.92 (d, 1H, J= 4.8 Hz), 7.63-7.48 (m, 3H), 7.30 (t, 1H, J= 1.8 Hz), 7.22 (dd, 1H, J= 1.8 and 7.5 Hz), 6.95 (t, 1H, J= 8.1 Hz), 6.32 (dd, 1H, J= 1.2 and 8.1 Hz), 4.29 (s, 2H), 2.62 (d, 1H, J= 4.8 Hz); LCMS: purity: 100%; MS (m/e): 536(MH⁺).

7.3.837 5-Fluoro-N2-[3-[(N-methylamino)carbonylmethyleneoxy]phenyl]-N4-(3-methoxy-4-methylphenyl)-2,4-pyrimidinediamine (R926902)

In like manner to the preparation of 5-fluoro-N4-(3-hydroxyphenyl)-N2-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine, 2-Chloro-5-fluoro-N4-(3-methoxy-4-methylphenyl)-4-pyrimidineamine and 3-methoxy-4-methylaniline were reacted to provide 5-fluoro-N2-[3-[(N-methylamino)carbonylmethyleneoxy]phenyl]-N4-(3-methoxy-4-methylphenyl)-2,4-pyrimidinediamine. ¹H NMR (DMSO-*d*₆): δ 9.78 (bs, 1H), 9.63 (bs, 1H), 8.15 (d, 1H, J= 4.5 Hz), 7.94 (d, 1H, J= 4.5 Hz), 7.94 (d, 1H, J= 4.5 Hz), 7.30 (dd, 1H, J= 1.8 and 8.4 Hz), 7.25-7.04 (m, 5H), 6.57 (d, 1H, J= 8.1 Hz), 4.31 (s, 2H), 3.66 (s, 3H), 2.62 (d, 1H, J= 4.8 Hz), 2.09 (s, 3H); LCMS: purity: 95%; MS (m/e): 412(MH⁺).

7.3.838 5-Fluoro-N4-(3-hydroxyphenyl)-N2-[2-(methoxycarbonyl)-(1H)-indol-6-yl]-2,4-pyrimidinediamine (R926903)

In like manner to the preparation of 5-fluoro-N4-(3-hydroxyphenyl)-N2-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-(3-hydroxyphenyl)-4-pyrimidineamine and 6-amino-2-(methoxycarbonyl)-(1H)-

indole were reacted to provide 5-fluoro-N4-(3-hydroxyphenyl)-N2-[2-(methoxycarbonyl)-(1H)-indol-6-yl]-2,4-pyrimidinediamine. ¹H NMR (DMSO-*d*₆): δ 11.53 (s, 1H), 9.37 (s, 1H), 9.18 (d, 2H, J= 9.9 Hz), 8.08 (d, 1H, J= 3.6 Hz), 7.96 (bs, 1H), 7.46 (d, 1H, J= 9.0 Hz), 7.39-7.35 (m, 2H), 7.16 (t, 1H, J= 2.4 Hz), 7.10-7.04 (m, 2H), 6.48 (dd, 1H, J= 2.4 and 7.5 Hz), 3.82 (s, 3H); LCMS: purity: 95%; MS (m/e): 394(MH⁺).

7.3.839 5-Fluoro-N2-[3-[(N-methylamino)carbonylmethyleneoxy]phenyl]-N4-[2-(methoxycarbonyl)-(1H)-indol-6-yl]-2,4-pyrimidinediamine (R926904)

In like manner to the preparation of 5-fluoro-N4-(3-hydroxyphenyl)-N2-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine, 2-chloro-5-fluoro N4-[2-(methoxycarbonyl)-(1H)-indol-6-yl]-4-pyrimidineamine and 3-[(N-methylamino)carbonylmethyleneoxy]aniline were reacted to provide 5-fluoro-N2-[3-[(N-methylamino)carbonylmethyleneoxy]phenyl]-N4-[2-(methoxycarbonyl)-(1H)-indol-6-yl]-2,4-pyrimidinediamine. ¹H NMR (CDCl₃): δ 9.05 (bs, 1H), 8.35 (s, 1H), 8.00 (bs, 1H), 7.66-7.62 (m, 2H), 7.27-7.17 (m, 3H), 7.01-6.90 (m, 3H), 6.64 (dd, 1H, J= 2.4 and 8.1 Hz), 6.40 (bs, 1H), 4.49 (s, 2H), 3.94 (s, 3H), 2.75 (d, 3H, J= 5.1 Hz); LCMS: purity: 86%; MS (m/e): 465(MH⁺).

7.3.840 N4-[3-[[4-(Ethoxycarbonyl)piperidino]methyl]phenyl]-5-fluoro-N2-[3-[(N-methylamino)carbonylmethyleneoxy]phenyl]-2,4-pyrimidinediamine (R926905)

In like manner to the preparation of 5-fluoro-N4-(3-hydroxyphenyl)-N2-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-[3-[[4-(ethoxycarbonyl)piperidino]methyl]phenyl]-4-pyrimidineamine and 3-[(N-methylamino)carbonylmethyleneoxy]aniline were reacted to provide 5-fluoro-N4-[3-[[4-(ethoxycarbonyl)piperidino]methyl]phenyl]-N2-[3-[(N-methylamino)carbonylmethyleneoxy]phenyl]-2,4-pyrimidinediamine. ¹H NMR (DMSO-*d*₆): 9.33 (s, 1H), 9.20 (s, 1H), 8.09 (d, 1H, J= 4.2 Hz), 7.93 (d, 1H, J= 4.8 Hz), 7.82 (d, 1H, J= 8.1 Hz), 7.55 (s, 1H), 7.35 (t, 1H, J= 2.4 Hz), 7.29-7.22 (m, 2H), 7.09 (t, 1H, J= 8.1 Hz), 6.96 (d, 1H, J= 7.8 Hz), 6.47 (dd, 1H, J= 2.4 and 8.1 Hz), 4.32 (s, 2H), 4.02 (q, 2H, J= 6.9 Hz), 3.39 (s, 2H), 2.73 (bd, 2H, J= 11.1 Hz), 2.63 (d, 3H, J= 4.5 Hz), 2.30-2.20 (m, 1H),

1.94 (t, 2H, J= 11.1 Hz), 1.74 (d, 2H, J= 9.9 Hz), 1.60-1.50 (m, 2H), 1.14 (t, 3H, J= 6.9 Hz); LCMS: purity: 99%; MS (m/e): 537(M - CH₂⁺).

7.3.841 N2-[3-(Ethoxycarbonyl-1,1-dimethylmethylenoxy)phenyl]-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine (R926906)

In like manner to the preparation of 5-fluoro-N4-(3-hydroxyphenyl)-N2-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)methylenoxyphenyl]-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-(3-hydroxyphenyl)-4-pyrimidineamine and 3-(ethoxycarbonyl-1,1-dimethylmethylenoxy)aniline were reacted to provide N2-[3-(ethoxycarbonyl-1,1-dimethylmethylenoxy)phenyl]-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine. ¹H NMR (CD₃OD): δ 7.91 (d, 1H, J= 4.8 Hz), 7.20-7.03 (m, 6H), 6.67 (td, 1H, J= 2.1 and 7.5 Hz), 6.57-6.53 (m, 1H), 4.19 (q, 2H, J= 6.9 Hz), 1.53 (s, 6H), 1.20 (t, 3H, J= 6.9 Hz); ¹⁹F NMR (282 MHz, CD₃OD): -46120; LCMS: purity: 91%; MS (m/e): 427(MH⁺).

7.3.842 N2-[3-(Ethoxycarbonyl-1,1-dimethylmethylenoxy)phenyl]-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R926907)

In like manner to the preparation of 5-fluoro-N4-(3-hydroxyphenyl)-N2-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)methylenoxyphenyl]-2,4-pyrimidinediamine, 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine and 3-(ethoxycarbonyl-1,1-dimethylmethylenoxy)aniline were reacted to provide N2-[3-(ethoxycarbonyl-1,1-dimethylmethylenoxy)phenyl]-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine. ¹H NMR (CDCl₃): δ 7.92 (d, 1H, J= 3.0 Hz), 7.21-7.08 (m, 4H), 7.00 (dd, 1H, J= 2.4 and 8.4 Hz), 6.93 (bs, 1H), 6.86 (d, 1H, J= 8.7 Hz), 6.99 (d, 1H, J= 2.4 Hz), 6.45 (ddd, 1H, J= 1.2, 1.2, and 7.8 Hz), 4.27 (s, 4H), 4.23 (q, 2H, J= 6.9 Hz), 1.60 (s, 6H), 1.23 (t, 3H, J= 6.9 Hz); ¹⁹F NMR (282 MHz, CDCl₃): -47216; LCMS: purity: 85%; MS (m/e): 469(MH⁺).

7.3.843 N2-[3-(Ethoxycarbonyl-1,1-dimethylmethylenoxy)phenyl]-5-fluoro-N4-(3-hydroxy-4-methylphenyl)-2,4-pyrimidinediamine (R926908)

In like manner to the preparation of 5-fluoro-N4-(3-hydroxyphenyl)-N2-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)methylenoxyphenyl]-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-(2-hydroxy-4-methylphenyl)-4-pyrimidineamine and 3-(ethoxycarbonyl-1,1-dimethylmethylenoxy)aniline were reacted to provide N2-[3-(ethoxycarbonyl-1,1-

dimethylmethylenedioxy)phenyl]-5-fluoro-N4-(3-hydroxy-4-methylphenyl)-2,4-pyrimidinediamine. ¹H NMR (CDCl₃): δ 7.86 (bs, 1H), 7.80 (bs, 1H), 7.53 (s, 1H), 7.16-6.86 (m, 4H), 6.54 (d, 2H, J= 7.5 Hz), 4.21 (q, 2H, J= 6.9 Hz), 3.48 (s, 2H), 2.20 (s, 3H), 1.60 (s, 6H), 1.22 (t, 3H, J= 6.9 Hz); ¹⁹F NMR (282 MHz, CDCl₃): -46808; LCMS: purity: 96%; MS (m/e): 441(MH⁺).

7.3.844 N2-[3-(Ethoxycarbonyl-1,1-dimethylmethylenedioxy)phenyl]-5-fluoro-N4-[(1H)-indol-6-yl]-2,4-pyrimidinediamine (R926909)

In like manner to the preparation of 5-fluoro-N4-(3-hydroxyphenyl)-N2-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)methylenedioxyphenyl]-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-[(1H)indol-6-yl]-4-pyrimidineamine and 3-(ethoxycarbonyl-1,1-dimethylmethylenedioxy)aniline were reacted to provide N2-[3-(Ethoxycarbonyl-1,1-dimethylmethylenedioxy)phenyl]-5-fluoro-N4-[(1H)-indol-6-yl]-2,4-pyrimidinediamine. ¹H NMR (CDCl₃): δ 9.43 (bs, 1H), 8.64 (s, 1H), 7.92 (d, 1H, J= 3.6 Hz), 7.66 (t, 1H, J= 2.4 Hz), 7.54 (d, 1H, J= 8.4 Hz), 7.44 (s, 1H), 7.19 (t, 1H, J= 3.0 Hz), 7.15 (d, 1H, J= 8.1 Hz), 6.96 (d, 1H, J= 3.0 Hz), 6.80 (dd, 1H, J= 1.8 and 7.5 Hz), 6.77 (dd, 1H, J= 1.8 and 8.1 Hz), 6.52 (dd, 1H, J= 1.8 and 7.5 Hz), 6.49-6.46 (m, 1H), 4.32 (q, 2H, J= 7.2 Hz), 1.57 (s, 6H), 1.31 (t, 3H, J= 7.2 Hz); ¹⁹F NMR (282 MHz, CDCl₃): -47190; LCMS: purity: 93%; MS (m/e): 450(MH⁺).

7.3.845 5-Fluoro-N4-(3-hydroxyphenyl)-N2-[3-[(N-methylamino)carbonyl-1,1-dimethylmethylenedioxy]phenyl]-2,4-pyrimidinediamine (R926913)

In like manner to the preparation of 5-fluoro-N4-(3-hydroxyphenyl)-N2-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)methylenedioxyphenyl]-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-(3-hydroxyphenyl)-4-pyrimidineamine and 3-(N-methylamino)carbonyl-1,1-dimethylmethylenedioxy)aniline were reacted to provide 5-fluoro-N4-(3-hydroxyphenyl)-N2-[3-[(N-methylamino)carbonyl-1,1-dimethylmethylenedioxy]phenyl]-2,4-pyrimidinediamine. ¹H NMR (DMSO-*d*₆): δ 9.35 (s, 1H), 9.20 (s, 1H), 9.17 (s, 1H), 8.07 (d, 1H, J= 3.3 Hz), 7.93 (d, 1H, J= 3.9 Hz), 7.40-7.29 (m, 3H), 7.13-7.02 (m, 3H), 6.47 (d, 1H, J= 7.5 Hz), 6.33 (d, 1H, J= 7.5 Hz), 2.60 (s, 3H), 1.37 (s, 6H); LCMS: purity: 97%; MS (m/e): 412(MH⁺).

7.3.846 5-Fluoro-N4-(1,2,3,4-tetrahydroisoquin-7-yl)-N2-[3-[(N-methylamino)carbonylmethyleneoxy]phenyl]-2,4-pyrimidinediamine (R926914)

In like manner to the preparation of 5-fluoro-N4-(3-hydroxyphenyl)-N2-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-[2-(t-butoxycarbonyl)-1,2,3,4-tetrahydroisoquinolin-7-yl]-4-pyrimidineamine and 3-[(N-methylamino)carbonylmethyleneoxy]aniline were reacted to provide 5-fluoro-N4-(1,2,3,4-tetrahydroisoquin-7-yl)-N2-[3-[(N-methylamino)carbonylmethyleneoxy]phenyl]-2,4-pyrimidinediamine. ¹H NMR (DMSO-*d*₆): δ 7.90 (d, 1H, J= 3.3 Hz), 7.47 (d, 1H, J= 2.4 Hz), 7.42-7.37 (m, 2H), 7.16 (t, 1H, J= 8.4 Hz), 7.10-7.04 (m, 2H), 6.50 (ddd, 1H, J= 1.2, 2.4, and 8.1 Hz), 4.26 (s, 2H), 3.93 (s, 2H), 3.12 (t, 2H, J= 6.3 Hz), 2.84-2.76 (m, 5H), ; ¹⁹F NMR (282 MHz, CD₃OD): -47489; LCMS: purity: 87%; MS (m/e): 423(MH⁺).

7.3.847 N4-(3,4-Ethylenedioxyphenyl)-5-fluoro- N2-[3-[(N-methylamino)carbonyl-1,1-dimethylmethyleneoxy]phenyl]-2,4-pyrimidinediamine (R926915)

In like manner to the preparation of 5-fluoro-N4-(3-hydroxyphenyl)-N2-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine, 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine and 3-(N-methylamino)carbonyl-1,1-dimethylmethyleneoxyaniline were reacted to provide N4-(3,4-Ethylenedioxyphenyl)-5-fluoro- N2-[3-[(N-methylamino)carbonyl-1,1-dimethylmethyleneoxy]phenyl]- 2,4-pyrimidinediamine. ¹H NMR (CD₃OD): δ 7.26 (t, 1H, J= 7.5 Hz), 7.19 (d, 1H, J= 9.3 Hz), 7.13 (d, 1H, J= 2.4 Hz), 7.06 (dd, 1H, J= 2.4 and 8.7 Hz), 7.04-7.03 (m, 1H), 6.83 (d, 1H, J= 9.0 Hz), 6.75 (d, 1H, J= 7.2 Hz), 4.25 (s, 4H), 2.76 (s, 3H), 1.43 (s, 6H); LCMS: purity: 97%; MS (m/e): 454(MH⁺).

7.3.848 5-Fluoro-N4-[3-[(N-allylamino)carbonyloxy]phenyl]-N2-[3-[(N-methylamino)carbonylmethyleneoxy]phenyl]- 2,4-pyrimidinediamine (R926917)

A mixture of 5-fluoro-N4-(3-hydroxyphenyl)-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (20 mg, 0.052 mmol), allyl isocyanate (13mg, 0.16 mmol), and 2-(N,N-dimethylamino)pyridine (18 mg, 0.15 mmol) in anhydrous THF (1 mL) were heated at 60°C in a sealed vial for 2 days. The reaction was diluted with ethyl acetate and washed with 1N HCl and brine. Concentration gave an oily residue which was

purified by preparative TLC (5% methanol/dichloromethane) to give the product 5-fluoro-N4-[3-[(N-allylamino)carbonyloxy]phenyl]-N2-[3-[(N-methylamino)carbonylmethyleneoxy]phenyl]-2,4-pyrimidinediamine. ¹H NMR (CD₃OD): δ 7.93 (d, 1H, J= 3.6 Hz), 7.62-7.55 (m, 2H), 7.32 (s, 1H), 7.30 (t, 1H, J= 8.1 Hz), 7.19-7.15 (m, 2H), 6.82 (dd, 1H, J= 2.4 and 8.1 Hz), 6.61 (m, 1H), 5.96-5.82 (m, 1H), 5.24 (dd, 1H, J= 1.8 and 16.8 Hz), 5.13 (dd, 1H, J= 1.8 and 11.7 Hz), 4.41 (s, 2H), 3.79 (d, 1H, J= 5.4 Hz), 2.80 (s, 3H); ¹⁹F NMR (282 MHz, CD₃OD): -47357; LCMS: purity: 99%; MS (m/e): 468(MH⁺).

7.3.849 5-Fluoro-N2-[3-[(N-methylamino)carbonylmethyleneoxy]phenyl]-N4-[3-[[N-isopropylamino)carbonyl]-N-isopropylamino)carbonyloxy]phenyl]-2,4-pyrimidinediamine (R926916)

In a like manner to the preparation of 5-fluoro-N4-[3-[(N-allylamino)carbonyloxy]phenyl]-N2-[3-[(N-methylamino)carbonylmethyleneoxy]phenyl]-2,4-pyrimidinediamine and isopropyl isocyanate were reacted to provide 5-fluoro-N2-[3-[(N-methylamino)carbonylmethyleneoxy]phenyl]-N4-[3-[[N-isopropylamino)carbonyl]-N-isopropylamino)carbonyloxy]phenyl]-2,4-pyrimidinediamine. ¹H NMR (DMSO-*d*₆): δ 9.40 (bs, 1H), 9.27 (bs, 1H), 8.12 (d, 1H, J= 3.6 Hz), 7.94 (d, 1H, J= 3.9 Hz), 7.78 (d, 1H, J= 8.7 Hz), 7.64 (d, 1H, J= 7.5 Hz), 7.46 (s, 1H), 7.36-7.26 (m, 3H), 7.12 (t, 1H, J= 8.1 Hz), 6.81-6.74 (m, 1H), 6.47 (dd, 1H, J= 2.4 and 8.1 Hz), 5.43 (d, 1H, J= 3.9 Hz), 4.36 (s, 2H), 3.65-3.55 (m, 2H), 3.14 (s, 2H), 2.63 (d, 3H, J= 3.9 Hz), 1.10 (d, 6H, J= 7.2 Hz), 0.97 (d, 6H, J= 6.6 Hz).

7.3.850 N4-[3-[[N-(Ethoxycarbonylmethyl)amino]carbonyloxy]phenyl]-5-fluoro-N2-[3-[(N-methylamino)carbonylmethyleneoxy]phenyl]-2,4-pyrimidinediamine (R926918)

In a like manner to the preparation of 5-fluoro-N4-[3-[(N-allylamino)carbonyloxy]phenyl]-N2-[3-[(N-methylamino)carbonylmethyleneoxy]phenyl]-2,4-pyrimidinediamine and ethyl isocyanatoacetate were reacted to provide N4-[3-[[N-(ethoxycarbonylmethyl)amino]carbonyloxy]phenyl]-5-fluoro-N2-[3-[(N-methylamino)carbonylmethyleneoxy]phenyl]-2,4-pyrimidinediamine. ¹H NMR (CD₃OD): δ 7.94 (d, 1H, J= 3.3 Hz), 7.69 (t, 1H, J= 1.8 Hz), 7.56 (ddd, 1H, J= 1.2, 1.2, and 8.1 Hz), 7.35 (m, 1H), 7.31 (t, 1H, J= 8.1 Hz), 7.18 (d, 1H, J= 2.4 Hz), 7.17 (d, 1H, J= 1.2 Hz), 6.84 (dd, 1H, J= 2.4 and 8.1 Hz), 6.63-6.58 (m, 1H), 4.42 (s, 2H), 4.20 (q, 2H, J= 7.2 Hz), 3.93

(s, 2H), 2.80 (s, 3H), 1.27 (t, 3H, J= 7.2 Hz); ^{19}F NMR (282 MHz, CD_3OD): -47371; LCMS: purity: 89%; MS (m/e): 513(MH^+).

7.3.851 N4-[3-[(N-(Ethylamino)carbonyloxy]phenyl]-5-fluoro-N2-[3-[(N-methylamino)carbonylmethyleneoxy]phenyl]-2,4-pyrimidinediamine (R926919)

In a like manner to the preparation of 5-fluoro-N4-[3-[(N-allylamino)carbonyloxy]phenyl]-N2-[3-[(N-methylamino)carbonylmethyleneoxy]phenyl]-2,4-pyrimidinediamine and ethyl isocyanate were reacted to provide N4-[3-[(N-(ethylamino)carbonyloxy]phenyl]-5-fluoro-N2-[3-[(N-methylamino)carbonylmethyleneoxy]phenyl]-2,4-pyrimidinediamine. ^1H NMR (CD_3OD): δ 7.94 (d, 1H, J= 3.3 Hz), 6.84-6.79 (m, 2H), 7.61-7.55 (m, 2H), 6.62-6.56 (m, 2H), 7.33-7.27 (m, 1H), 7.19-7.17 (m, 1H), 4.41 (s, 2H), 3.23 (q, 2H, J= 7.2 Hz), 2.80 (s, 3H), 1.17 (t, 3H, J= 7.2 Hz); ^{19}F NMR (282 MHz, CD_3OD): -47378; LCMS: purity: 100%; MS (m/e): 455(MH^+).

7.3.852 5-Fluoro-N2-[3-[(N-methylamino)carbonylmethyleneoxy]phenyl]-N4-(4-methyl-3-trifluoromethylphenyl)-2,4-pyrimidinediamine (R926922)

In like manner to the preparation of 5-fluoro-N4-(3-hydroxyphenyl)-N2-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-(4-methyl-3-trifluoromethylphenyl)-4-pyrimidineamine and 3-[(N-methylamino)carbonylmethyleneoxy]aniline were reacted to provide 5-fluoro-N2-[3-[(N-methylamino)carbonylmethyleneoxy]phenyl]-N4-(4-methyl-3-trifluoromethylphenyl)-2,4-pyrimidinediamine. ^1H NMR ($\text{DMSO}-d_6$): δ 9.79 (bs, 1H), 9.48 (bs, 1H), 8.17 (d, 1H, J= 4.2 Hz), 8.10 (d, 1H, J= 6.3 Hz), 7.96 (d, 1H, J= 4.8 Hz), 7.89 (d, 1H, J= 2.1 Hz), 7.38 (d, 1H, J= 9.0 Hz), 7.26-7.20 (m, 2H), 7.11 (t, 1H, J= 8.4 Hz), 6.53 (d, 1H, J= 8.4 Hz), 4.33 (s, 2H), 2.62 (d, 3H, J= 4.8 Hz), 2.39 (s, 3H); LCMS: purity: 94%; MS (m/e): 450(MH^+).

7.3.853 5-Fluoro-N4-(4-fluoro-3-methylphenyl)-N2-[3-[(N-methylamino)carbonylmethyleneoxy]phenyl]-2,4-pyrimidinediamine (R926923)

In like manner to the preparation of 5-fluoro-N4-(3-hydroxyphenyl)-N2-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-(4-fluoro-3-methylphenyl)-4-pyrimidineamine and 3-[(N-methylamino)carbonylmethyleneoxy]aniline were reacted to provide 5-Fluoro-N4-(4-

fluoro-3-methylphenyl)-N2-[3-[(N-methylamino)carbonylmethyleneoxy]phenyl]-2,4-pyrimidinediamine. ¹H NMR (DMSO-*d*₆): δ 9.67 (bs, 1H), 9.51 (bs, 1H), 8.14 (d, 1H, J= 4.8 Hz), 7.95 (d, 1H, J= 4.2 Hz), 7.64 (dd, 1H, J= 2.7 and 6.9 Hz), 7.57-7.50 (m, 1H), 7.23-7.06 (m, 4H), 6.55 (d, 1H, J= 7.5 Hz), 4.33 (s, 2H), 2.63 (d, 3H, J= 4.8 Hz), 2.19 (s, 3H);

5 LCMS: purity: 94%; MS (m/e): 400(MH⁺).

7.3.854 5-Fluoro-N2-[3-[(N-methylamino)carbonylmethyleneoxy]phenyl]-N4-(3-trifluoromethylthiophenyl)-2,4-pyrimidinediamine (R926925)

In like manner to the preparation of 5-fluoro-N4-(3-hydroxyphenyl)-N2-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-(3-trifluoromethylthiophenyl)-4-pyrimidineamine and 3-[(N-methylamino)carbonylmethyleneoxy]aniline were reacted to provide 5-fluoro-N2-[3-[(N-methylamino)carbonylmethyleneoxy]phenyl]-N4-(3-trifluoromethylthiophenyl)-2,4-pyrimidinediamine. ¹H NMR (DMSO-*d*₆): δ 9.83 (bs, 1H), 9.49 (bs, 1H), 8.21-8.15 (m, 2H), 8.01 (s, 1H), 7.94 (bs, 1H), 7.49 (t, 1H, J= 7.8 Hz), 7.38 (d, 1H, J= 7.8 Hz), 7.29 (s, 1H), 7.22 (d, 1H, J= 7.5 Hz), 7.14 (t, 1H, J= 8.4 Hz), 6.54 (d, 1H, J= 9.9 Hz), 4.34 (s, 2H), 2.62 (d, 3H, J= 4.8 Hz); LCMS: purity: 98%; MS (m/e): 468(MH⁺).

7.3.855 N2-[3,5-Bis(methoxycarbonylmethyleneoxy)phenyl]-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine (R926926)

In like manner to the preparation of 5-fluoro-N4-(3-hydroxyphenyl)-N2-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-(3-hydroxyphenyl)-4-pyrimidineamine and 3,5-bis(methoxycarbonylmethyleneoxy)aniline were reacted to provide N2-[3,5-bis(methoxycarbonylmethyleneoxy)phenyl]-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine. ¹H NMR (CD₃OD): δ 7.92 (d, 1H, J= 4.2 Hz), 7.20-7.10 (m, 3H), 6.92 (d, 2H, J= 2.4 Hz), 6.52 (ddd, 1H, J= 1.8, 1.8, and 7.5 Hz), 6.12 (t, 1H, J= 2.4 Hz), 4.55 (s, 4H), 3.77 (s, 6H); ¹⁹F NMR (282 MHz, CD₃OD): -47342; LCMS: purity: 92%; MS (m/e): 473(MH⁺).

7.3.856 5-Fluoro-N2-[3-hydroxy-5-(methoxycarbonylmethyleneoxy)phenyl]-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine (R926927)

In a like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro -N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-(3-hydroxyphenyl)-4-pyrimidineamine and 3-hydroxy-5-(methoxycarbonylmethyleneoxy)aniline were reacted to produce 5-fluoro-N2-[3-hydroxy-5-(methoxycarbonylmethyleneoxy)phenyl]-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine. ¹H NMR (DMSO-*d*₆): δ 8.13 (d, 1H, J= 4.8 Hz), 7.37-7.33 (m, 1H), 7.11 (t, 1H, J= 8.4 Hz), 7.07-7.05 (m, 1H), 6.73-6.65 (m, 2H), 6.51 (dd, 1H, J= 2.1 and 8.1 Hz), 5.97 ((s, 1H), 4.59 (s, 2H), 3.67 (s, 3H); LCMS: purity: 93%; MS (m/e): 401(MH⁺).

7.3.857 N2-[3-[(N-Ethylamino)carbonyloxy]phenyl]-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine (R926928)

In like manner to the preparation of 5-fluoro-N4-(3-hydroxyphenyl)-N2-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-(3-hydroxyphenyl)-4-pyrimidineamine and 3-[(N-ethylamino)carbonyloxy]aniline were reacted to provide N2-[3-[(N-ethylamino)carbonyloxy]phenyl]-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine. ¹H NMR (CDCl₃): δ 7.92 (d, 1H, J= 3.0 Hz), 7.67-7.55 (m, 2H), 7.24 (t, 1H, J= 7.5 Hz), 7.16 (t, 1H, J= 7.5 Hz), 7.07-6.98 (m, 2H), 6.84-6.79 (m, 2H), 6.67 (m, 2H), 6.60 (d, 1H, J= 7.5 Hz), 5.22-5.14 (m, 1H), 3.36-3.27 (m, 2H), 2.95 (s, 1H), 2.88 (s, 1H), 1.20 (t, 3H, J= 7.5 Hz); ¹⁹F NMR (282 MHz, CDCl₃): -47012; LCMS: purity: 99%; MS (m/e): 384(MH⁺).

7.3.858 5-Fluoro-N2-[3-hydroxy-5-[(N-methylamino)carbonylmethyleneoxy]phenyl]-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine (R926929)

A solution of 5-fluoro-N2-[3-hydroxy-5-(methoxycarbonylmethyleneoxy)phenyl]-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine (56 mg, 0.13 mmol), methylamine hydrochloride (90 mg, 1.3 mmol), and diisopropylethylamine (0.12 mL, 0.70 mmol) in methanol (2 mL) was heated at 100°C for 8h. The cooled reaction mixture was poured into 1N HCl (20 mL) saturated with NaCl, and extracted with ethyl acetate. Purification by preparative TLC (5% methanol/dichloromethane) gave the product, 5-fluoro-N2-[3-hydroxy-5-[(N-methylamino)carbonylmethyleneoxy]phenyl]-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine. ¹H NMR (DMSO-*d*₆): δ 9.29 (bs, 1H), 9.16 (s, 1H), 9.01 (s, 1H), 8.06

(d, 1H, J= 3.3 Hz), 7.87 (d, 1H, J= 4.8 Hz), 7.42 (dd, 1H, J= 1.5 and 8.1 Hz), 7.13-7.05 (m, 2H), 6.89-6.81 (m, 2H), 6.45 (dd, 1H, J= 2.4 and 8.4 Hz), 5.92 (t, 1H, J= 2.4 Hz), 4.28 (s, 2H), 3.30(bs, 1H), 2.63 (s, 3H); LCMS: purity: 94%; MS (m/e): 400(MH⁺).

7.3.859 N2-[3,5-Bis[(N-methylamino)carbonylmethyleneoxy]phenyl]-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine (R926930)

In a like manner to the preparation of 5-fluoro-N2-[3-hydroxy-5-[(N-methylamino)carbonylmethyleneoxy]phenyl]-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine, N2-[3,5-bis(methoxycarbonylmethyleneoxy)phenyl]-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine, methylamine hydrochloride, and diisopropylethylamine were reacted to give N2-[3,5-Bis[(N-methylamino)carbonylmethyleneoxy]phenyl]-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine. ¹H NMR (CD₃OD): δ 7.91 (bs, 1H), 7.25 (t, 1H, J= 1.8 Hz), 7.14-7.11 (m, 1H), 6.98 (s, 1H), 6.97 (s, 1H), 6.55-6.50 (m, 1H), 6.26-6.23 (m, 1H), 4.39 (s, 4H), 2.81 (s, 6H); ¹⁹F NMR (282 MHz, CD₃OD): -47307; LCMS: purity: 99%; MS (m/e): 471=(MH⁺).

7.3.860 5-Fluoro-N4-[(1H)-indol-5-yl]-N2-[3-[(N-methylamino)carbonylmethyleneoxy]phenyl]-2,4-pyrimidinediamine (R926931)

In like manner to the preparation of 5-fluoro-N4-(3-hydroxyphenyl)-N2-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-[(1H)-indol-5-yl]-4-pyrimidineamine and 3-[(N-methylamino)carbonylmethyleneoxy]aniline were reacted to provide 5-fluoro-N4-[(1H)-indol-5-yl]-N2-[3-[(N-methylamino)carbonylmethyleneoxy]phenyl]-2,4-pyrimidinediamine. ¹H NMR (DMSO-*d*₆): δ 11.09 (bs, 1H), 9.93 (bs, 1H), 9.67 (bs, 1H), 8.12 (d, 1H, J= 4.81 Hz), 7.94-7.82 (m, 2H), 7.37-7.22 (m, 4H), 7.13 (bs, 1H), 7.07 (t, 1H, J= 8.1 Hz), 6.58 (d, 1H, J= 7.8 Hz), 6.37 (s, 1H), 4.32 (s, 2H), 2.61 (d, 3H, J= 4.2 Hz); LCMS: purity: 92%; MS (m/e): 407(MH⁺).

7.3.861 5-Fluoro-N2-(3-hydroxyphenyl)-N4-[(1H)-indol-5-yl]-2,4-pyrimidinediamine (R926932)

In like manner to the preparation of 5-fluoro-N4-(3-hydroxyphenyl)-N2-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine, 2-chloro-5-

fluoro-N4-[(1H)-indol-5-yl]-4-pyrimidineamine and 3-hydroxyaniline were reacted to provide 5-fluoro-N2-(3-hydroxyphenyl)-N4-[(1H)-indol-5-yl]-2,4-pyrimidinediamine.

¹H NMR (DMSO-*d*₆): δ 11.13 (s, 1H), 10.25 (bs, 1H), 9.87 (bs, 1H), 9.43 (bs, 1H), 8.16 (d, 1H, J= 5.1 Hz), 7.89 (d, 1H, J= 0.09 Hz), 7.39-7.27 (m, 3H), 7.03-6.94 (m, 2H), 6.83 (s, 1H), 6.48 (d, 1H, J= 7.5 Hz), 6.40 (t, 1H, J= 2.1 Hz); LCMS: purity: 92%; MS (m/e): 336(MH⁺).

7.3.862 5-Fluoro-N4-[(1H)-indol-6-yl]-N2-[3-[(N-methylamino)carbonyl]phenyl]-2,4-pyrimidinediamine (R926933)

In like manner to the preparation of 5-fluoro-N4-(3-hydroxyphenyl)-N2-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-[(1H)indol-6-yl]-4-pyrimidineamine and 3-[(N-methylamino)carbonyl]aniline were reacted to provide 5-fluoro-N4-[(1H)indol-6-yl]-N2-[3-[(N-methylamino)carbonyl]phenyl]-2,4-pyrimidinediamine. ¹H NMR (CD₃OD): δ 7.99 (t, 1H, J= 1.8 Hz), 7.89 (d, 1H, J= 3.6 Hz), 7.78-7.76 (m, 1H), 7.70 (ddd, 1H, J= 1.2, 2.4, and 8.4 Hz), 7.50 (d, 1H, J= 9.0 Hz), 7.31 (td, 1H, J= 1.2 and 7.5 Hz), 7.23-7.17 (m, 3H), 6.43 (dd, 1H, J= 1.2 and 3.6 Hz), 2.73 (s, 3H); ¹⁹F NMR (282 MHz, CD₃OD): -47513; LCMS: purity: 99%; MS (m/e): 377(MH⁺).

7.3.863 5-Fluoro-N4-[(1H)-indol-6-yl]-N2-[3-(N-morpholinocarbonyl)phenyl]-2,4-pyrimidinediamine (R926934)

In like manner to the preparation of 5-fluoro-N4-(3-hydroxyphenyl)-N2-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-[(1H)indol-6-yl]-4-pyrimidineamine and 3-(N-morpholinocarbonyl)aniline were reacted to provide 5-fluoro-N4-[(1H)-indol-6-yl]-N2-[3-(N-morpholinocarbonyl)phenyl]-2,4-pyrimidinediamine. ¹H NMR (CD₃OD): δ 7.96 (d, 1H, J= 4.8 Hz), 7.73 (t, 1H, J= 2.4 Hz), 7.66 (d, 1H, J= 1.2 Hz), 7.52 (d, 1H, J= 8.1 Hz), 7.49 (ddd, 1H, J= 0.09, 2.1, and 8.1 Hz), 7.33-7.26 (m, 2H), 7.19 (dd, 1H, J= 1.8 and 8.7 Hz), 7.12-7.06 (m, 1H), 6.45 (dd, 1H, J= 1.3 and 3.0 Hz), 3.62-3.15 (m, 8H); ¹⁹F NMR (282 MHz, CD₃OD): -46545; LCMS: purity: 91%; MS (m/e): 433(MH⁺).

7.3.864 N2-[3-[[4-(Ethoxycarbonyl)piperidino]carbonyl]phenyl]-5-fluoro-N4-[(1H)-indol-6-yl]-2,4-pyrimidinediamine (R926935)

In like manner to the preparation of 5-fluoro-N4-(3-hydroxyphenyl)-N2-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-[(1H)indol-6-yl]-4-pyrimidineamine and 3-[4-(ethoxycarbonyl)piperidino]aniline were reacted to provide N2-[3-[[4-(ethoxycarbonyl)piperidino]carbonyl]phenyl]-5-fluoro-N4-[(1H)-indol-6-yl]-2,4-pyrimidinediamine. ¹H NMR (CD₃OD): δ 7.99 (d, 1H, J= 5.1 Hz), 7.64-7.58 (m, 2H), 7.52 (d, 1H, J= 8.7 Hz), 7.48 (ddd, 1H, J= 1.2, 2.4, and 8.1 Hz), 7.34-7.27 (m, 2H), 7.19-7.13 (m, 2H), 6.46 (dd, 1H, J= 1.2 and 4.2 Hz), 4.40-4.27 (m, 1H), 4.13 (q, 2H, J= 6.9 Hz), 3.56-3.41 (m, 1H), 2.95-2.82 (m, 2H), 2.58-2.47 (m, 1H), 1.98-1.82 (m, 1H), 1.75-7.60 (m, 1H), 1.58-1.39 (m, 2H), 1.24 (t, 3H, J= 6.9 Hz); ¹⁹F NMR (282 MHz, CD₃OD): -46101; LCMS: purity: 90%; MS (m/e): 503(MH⁺).

7.3.865 5-Fluoro-N4-(3-hydroxyphenyl)-N2-[3-[(N-methylamino)carbonyl]phenyl]-2,4-pyrimidinediamine (R926936)

In like manner to the preparation of 5-fluoro-N4-(3-hydroxyphenyl)-N2-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-(3-hydroxyphenyl)-4-pyrimidineamine and 3-[(N-methylamino)carbonyl]aniline were reacted to provide 5-fluoro-N4-(3-hydroxyphenyl)-N2-[3-[(N-methylamino)carbonyl]phenyl]-2,4-pyrimidinediamine. ¹H NMR (CD₃OD): δ 8.01 (d, 1H, J= 5.4 Hz), 7.84 (t, 1H, J= 1.8 Hz), 7.68-7.61 (m, 2H), 7.45 (t, 1H, J= 8.4 Hz), 7.16-7.03 (m, 3H), 6.68 (td, 1H, J= 1.2 and 8.7 Hz), 2.90 (s, 3H); LCMS: purity: 95%; MS (m/e): 354(MH⁺).

7.3.866 5-Fluoro-N4-(3-hydroxyphenyl)-N2-[3-[(N-propylamino)carbonyl]phenyl]-2,4-pyrimidinediamine (R926937)

In like manner to the preparation of 5-fluoro-N4-(3-hydroxyphenyl)-N2-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-(3-hydroxyphenyl)-4-pyrimidineamine and 3-[(N-propylamino)carbonyl]aniline were reacted to provide 5-fluoro-N4-(3-hydroxyphenyl)-N2-[3-[(N-propylamino)carbonyl]phenyl]-2,4-pyrimidinediamine. ¹H NMR (CD₃OD): δ 8.00 (d, 1H, J= 5.4 Hz), 7.84 (t, 1H, J= 1.8 Hz), 7.69-7.59 (m, 2H), 7.44 (t, 1H, J= 7.5 Hz), 7.16-7.05 (m, 3H), 6.67 (td, 1H, J= 2.4 and 7.2 Hz), 3.34-3.29 (m, 2H), 1.65-1.56 (m, 2H), 0.96 (t, 3H, J=

7.5 Hz); ^{19}F NMR (282 MHz, CD_3OD): -46049; LCMS: purity: 94%; MS (m/e): 382(MH^+).

7.3.867 5-Fluoro-N4-(3-hydroxyphenyl)-N2-[3-(N-morpholinocarbonyl)phenyl]-2,4-pyrimidinediamine (R926938)

In like manner to the preparation of 5-fluoro-N4-(3-hydroxyphenyl)-N2-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-(3-hydroxyphenyl)-4-pyrimidineamine and 3-(N-morpholinocarbonyl)aniline were reacted to provide 5-fluoro-N4-(3-hydroxyphenyl)-N2-[3-(N-morpholinocarbonyl)phenyl]-2,4-pyrimidinediamine. ^1H NMR (CD_3OD): δ 7.93 (d, 1H, $J = 3.6$ Hz), 7.84 (t, 1H, $J = 1.8$ Hz), 7.62 (ddd, 1H, $J = 1.2, 2.4$, and 8.1 Hz), 7.32 (t, 1H, $J = 8.4$ Hz), 7.19-7.10 (m, 3H), 6.96 (dd, 1H, $J = 1.2$ and 7.8 Hz), 6.56 (ddd, 1H, $J = 1.2, 3.0$, and 6.9 Hz), 3.78-3.34 (m, 8H); ^{19}F NMR (282 MHz, CD_3OD): -47323; LCMS: purity: 100%; MS (m/e): 410(MH^+).

7.3.868 N2-[3-[[4-(Ethoxycarbonyl)piperidino]carbonyl]phenyl]-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine (R926939)

In like manner to the preparation of 5-fluoro-N4-(3-hydroxyphenyl)-N2-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-(3-hydroxyphenyl)-4-pyrimidineamine and 3-[[4-(ethoxycarbonyl)piperidino]carbonyl]aniline were reacted to provide N2-[3-[[4-(ethoxycarbonyl)piperidino]carbonyl]phenyl]-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine. ^1H NMR (CD_3OD): δ 7.92 (d, 1H, $J = 3.6$ Hz), 7.82 (s, 1H), 7.62 (td, 1H, $J = 1.2$ and 8.4 Hz), 7.30 (t, 1H, $J = 8.4$ Hz), 7.19-7.09 (m, 3H), 6.93 (d, 1H, $J = 7.5$ Hz), 6.55 (td, 1H, $J = 1.2$ and 7.5 Hz), 4.43 (bd, 1H, $J = 12.3$ Hz), 4.13 (q, 2H, $J = 6.9$ Hz), 3.7 (bd, 1H, $J = 11.7$ Hz), 3.10-2.92 (m, 2H), 2.67-2.55 (m, 1H), 2.06-1.50 (m, 4H), 1.24 (t, 3H, $J = 6.9$ Hz); ^{19}F NMR (282 MHz, CD_3OD): -47299; LCMS: purity: 99%; MS (m/e): 480(MH^+).

7.3.869 N4-[3-[[4-(Ethoxycarbonyl)piperidino]carbonyl]phenyl]-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine (R926940)

In like manner to the preparation of 5-fluoro-N4-(3-hydroxyphenyl)-N2-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine, 2-chloro-N4-[3-[[4-(ethoxycarbonyl)piperidino]carbonyl]phenyl]-5-fluoro-4-pyrimidineamine and 3-

hydroxyaniline were reacted to provide N4-[3-[[4-(ethoxycarbonyl)piperidino]carbonyl]phenyl]-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine. ¹H NMR (CD₃OD): δ 7.93 (d, 1H, J= 3.6 Hz), 7.89 (t, 1H, J= 1.8 Hz), 7.83 (td, 1H, J= 1.2 and 8.4 Hz), 7.41 (t, 1H, J= 7.8 Hz), 7.11-6.95 (m, 4H), 6.41 (td, 1H, J= 1.8 and 7.2 Hz), 4.44 (bd, 1H, J= 12.9 Hz), 4.10 (q, 2H, J= 7.2 Hz), 3.73 (bd, 1H, J= 12.3 Hz), 3.18-2.98 (m, 2H), 2.67-2.55 (m, 1H), 2.05-1.53 (m, 4H), 1.23 (t, 3H, J= 7.2 Hz); ¹⁹F NMR (282 MHz, CD₃OD): -47483; LCMS: purity: 99%; MS (m/e): 480(MH⁺).

7.3.870 N4-[3-[[4-(Ethoxycarbonyl)piperidino]carbonyl]phenyl]-5-fluoro-N2-[3-[(N-methylamino)carbonylmethyleneoxy]phenyl]-2,4-pyrimidinediamine (R926941)

In like manner to the preparation of 5-fluoro-N4-(3-hydroxyphenyl)-N2-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine, 2-chloro-N4-[3-[[4-(ethoxycarbonyl)piperidino]carbonyl]phenyl]-5-fluoro-4-pyrimidineamine and 3-[(N-methylamino)carbonylmethyleneoxy]aniline were reacted to provide N4-[3-[[4-(ethoxycarbonyl)piperidino]carbonyl]phenyl]-5-fluoro-N2-[3-[(N-methylamino)carbonylmethyleneoxy]phenyl]-2,4-pyrimidinediamine. ¹H NMR (CD₃OD): δ 7.95 (d, 1H, J= 3.3 Hz), 7.90 (t, 1H, J= 1.8 Hz), 7.80 (ddd, 1H, J= 0.09, 2.1, 8.1 Hz), 7.39 (t, 1H, J= 7.5 Hz), 7.31 (t, 1H, J= 1.2 Hz), 7.17-7.06 (m, 3H), 6.60-6.54 (m, 1H), 4.48-4.38 (m, 3H), 4.10 (q, 2H, J= 6.9 Hz), 3.78-3.65 (m, 1H), 3.17-2.95 (m, 2H), 2.79 (s, 3H), 2.65-2.53 (m, 1H), 2.01-1.52 (m, 4H), 1.22 (t, 3H, J= 6.9 Hz); ¹⁹F NMR (282 MHz, CD₃OD): -47309; LCMS: purity: 99%; MS (m/e): 551(MH⁺).

7.3.871 Reaction of 3-hydroxyaniline and 2-chloro-5-fluoro-N4-(1,2,3,4-tetrahydro-1-hydroxynaphthalen-7-yl)-4-pyrimidineamine

In like manner to the preparation of 5-fluoro-N4-(3-hydroxyphenyl)-N2-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-(1,2,3,4-tetrahydro-1-hydroxynaphthalen-7-yl)-4-pyrimidineamine and 3-hydroxyaniline were reacted to provide two products, R926942 and R926943.

7.3.872 N4-(1-Ethoxy-1,2,3,4-tetrahydronaphthalen-7-yl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine (R926942)

¹H NMR (DMSO-*d*₆): δ 9.23 (bs, 1H), 9.14 (bs, 1H), 8.97 (bs, 1H), 8.04 (d, 1H, J= 3.6 Hz), 7.71 (dd, 1H, J= 2.4 and 7.5 Hz), 7.56 (bs, 1H), 7.14-6.98 (m, 3H), 6.93 (t, 1H, J=

8.1 Hz), 6.29 (bd, 1H, J= 7.2 Hz), 4.35 (bs, 1H), 3.59-3.36 (m, 2H), 2.69-2.60 (m, 2H), 1.89-1.78 (m, 2H), 1.72-1.56 (m, 2H), 1.08 (t, 3H, J= 6.9 Hz); LCMS: purity: 96%; MS (m/e): 395(MH⁺).

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7.3.873 5-Fluoro-N4-(3,4-dihydronaphthalen-7-yl)-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine (R926943)

¹H NMR (DMSO-*d*₆): δ 9.19 (bs, 2H), 9.01 (s, 1H), 8.04 (d, 1H, J= 3.6 Hz), 7.56-7.46 (m, 2H), 7.16-7.03 (m, 3H), 6.94 (t, 1H, J= 8.1 Hz), 6.46 (d, 1H, J= 9.6 Hz), 6.03 (dd, 1H, J= 1.8 and 8.1 Hz), 6.09-6.01 (m, 1H), 2.69 (t, 2H, J= 8.4 Hz), 2.28-2.20 (m, 2H); ¹⁹F NMR (282 MHz, DMSO-*d*₆): -46541; LCMS: purity: 98%; MS (m/e): 349(MH⁺).

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7.3.874 5-Fluoro-N4-(3,4-dihydronaphthalen-7-yl)-N2-[3-[(N-methylamino)carbonylmethyleneoxy]phenyl]-2,4-pyrimidinediamine (R926944)

In like manner to the preparation of 5-fluoro-N4-(3-hydroxyphenyl)-N2-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-(1,2,3,4-tetrahydro-1-hydroxynaphthalen-7-yl)-4-pyrimidineamine and 3-[(N-methylamino)carbonylmethyleneoxy]aniline were reacted to provide 5-fluoro-N4-(3,4-dihydronaphthalen-7-yl)-N2-[3-[(N-methylamino)carbonylmethyleneoxy]phenyl]-2,4-pyrimidinediamine. ¹H NMR (DMSO-*d*₆): δ 8.07 (d, 1H, J= 3.9 Hz), 7.53-7.45 (m, 2H), 7.32-7.29 (m, 2H), 7.11-7.01 (m, 2H), 6.49-6.40 (m, 2H), 6.08-6.00 (m, 1H), 4.32 (s, 2H), 2.69 (t, 2H, J= 8.4 Hz), 2.62 (s, 3H); LCMS: purity: 99%; MS (m/e): 420(MH⁺).

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7.3.875 N4-(3-Chloro-4-methoxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine (R926945)

In a like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N4-(3-chloro-4-methoxyphenyl)-5-fluoro-4-pyrimidineamine and 3-hydroxyaniline were reacted to produce N4-(3-chloro-4-methoxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine. ¹H NMR (CD₃OD): δ 7.91 (d, 1H, J= 5.4 Hz), 7.71 (d, 1H, J= 2.4 Hz), 7.58 (dd, 1H, J= 3.0 and 9.0 Hz), 7.15 (t, 1H, J= 8.4 Hz), 7.06 (d, 1H, J= 8.7 Hz), 6.92 (td, 1H, J= 1.8 and 9.9 Hz), 6.88 (t, 1H, J= 1.8 Hz), 6.61 (ddd, 1H, J= 1.2, 2.4, and 8.1 Hz), 3.89 (s, 3H), ; ¹⁹F NMR (282 MHz, CD₃OD): -46612; LCMS: purity: 98%; MS (m/e): 362(MH⁺).

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7.3.876 N2,N4-Bis(3-chloro-4-methoxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R926946)

In a like manner to the preparation of N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, 2,4-dichloro-5-fluoropyrimidine and 3-chloro-4-methoxyaniline were reacted to provide N2,N4-Bis(3-chloro-4-methoxyphenyl)-5-fluoro-2,4-pyrimidinediamine. ¹H NMR (DMSO-*d*₆): δ 9.90 (bs, 1H), 9.68 (bs, 1H), 8.16 (d, 1H, J= 4.8 Hz), 7.72 (d, 1H, J= 2.4 Hz), 7.65 (d, 1H, J= 2.1 Hz), 7.58 (dd, 1H, J= 2.4 and 9.0 Hz), 7.38 (dd, 1H, J= 2.7 and 9.3 Hz), 7.12 (d, 1H, J= 8.7 Hz), 7.12 (d, 1H, J= 8.7 Hz), 7.05 (d, 1H, J= 8.7 Hz), 3.83 (s, 3H), 3.79 (s, 3H); LCMS: purity: 99%; MS (m/e): 410(MH⁺).

7.3.877 5-Fluoro-N4-(1,2,3,4-tetrahydro-1-oxonaphthalen-7-yl)-N2-[3-[(N-methylamino)carbonylmethyleneoxy]phenyl]-2,4-pyrimidinediamine (R926947)

In like manner to the preparation of 5-fluoro-N4-(3-hydroxyphenyl)-N2-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-(1,2,3,4-tetrahydro-1-oxo-naphthalen-7-yl)-4-pyrimidineamine and 3-[(N-methylamino)carbonylmethyleneoxy]aniline were reacted to provide 5-fluoro-N4-(1,2,3,4-tetrahydro-1-oxo-naphthalen-7-yl)-N2-[3-[(N-methylamino)carbonylmethyleneoxy]phenyl]-2,4-pyrimidinediamine. ¹H NMR (DMSO-*d*₆): δ 9.89 (bs, 1H), 9.55 (bs, 1H), 8.17 (d, 1H, J= 4.2 Hz), 8.04-7.93 (m, 3H), 7.32 (d, 1H, J= 8.7 Hz), 7.25-7.16 (m, 2H), 7.09 (t, 1H, J= 7.5 Hz), 6.52 (dd, 1H, J= 2.4 and 8.1 Hz), 4.28 (s, 2H), 2.90 (t, 2H, J= 6.0 Hz), 2.63 (d, 3H, J= 4.8 Hz), 2.59 (t, 2H, J= 6.6 Hz), 2.02 (t, 2H, J= 6.6 Hz); LCMS: purity: 93%; MS (m/e): 436(MH⁺).

7.3.878 5-Fluoro-N4-(1,2,3,4-tetrahydro-1-hydroxyiminonaphthalen-7-yl)-N2-[3-[(N-methylamino)carbonylmethyleneoxy]phenyl]-2,4-pyrimidinediamine (R926948)

A solution of 5-fluoro-N4-(1,2,3,4-tetrahydro-1-oxo-naphthalen-7-yl)-N2-[3-[(N-methylamino)carbonylmethyleneoxy]phenyl]-2,4-pyrimidinediamine (42 mg, 0.095 mmole) and hydroxylamine hydrochloride (8.5 mg, 0.12 mmole) in DMF (1 mL) was heated at 60°C for 12h. The reaction mixture was cooled to rt and then poured into brine (20 mL). A brown solid was collected by suction filtration and further purified by reverse phase chromatography to provide 5-fluoro-N4-(1,2,3,4-tetrahydro-1-hydroxyiminonaphthalen-7-yl)-N2-[3-[(N-methylamino)carbonylmethyleneoxy]phenyl]-2,4-pyrimidinediamine. ¹H NMR (DMSO-*d*₆): δ 8.13-8.05 (m, 2H), 7.99-7.92 (m, 2H), 7.77-7.72 (m, 1H), 7.33-7.21

(m, 2H), 7.14 (d, 1H, J= 8.7 Hz), 7.10-7.02 (m, 1H), 6.47 (dd, 1H, J= 2.4 and 7.5 Hz), 4.30 (s, 2H), 2.90 (t, 1H, J= 6.0 Hz), 2.70-2.40 (m, 6H), 2.07-1.98 (m, 1H), 1.74 (t, 1H, J= 6.6 Hz); LCMS: purity: 96%; MS (m/e): 451(MH⁺).

7.3.879 5-Fluoro-N4-(1,2,3,4-tetrahydro-1-hydroxynaphthalen-7-yl)-N2-[3-[(N-methylamino)carbonylmethyleneoxy]phenyl]-2,4-pyrimidinediamine (R926949)

To a 0°C suspension of 5-fluoro-N4-(1,2,3,4-tetrahydro-1-oxo-naphthalen-7-yl)-N2-[3-[(N-methylamino)carbonylmethyleneoxy]phenyl]-2,4-pyrimidinediamine (50mg, 0.11 mmol) in anhydrous THF (2.0 mL) was added lithiumborohydride (5 mg, 0.23 mmole).

The reaction mixture was warmed to rt, stirred for 8h, and then quenched with methanol. The reaction mixture was poured into water and then extracted with ethyl acetate.

Purification by preparative TLC (5% methanol/dichloromethane) provided 5-fluoro-N4-(1,2,3,4-tetrahydro-1-hydroxynaphthalen-7-yl)-N2-[3-[(N-methylamino)carbonylmethyleneoxy]phenyl]-2,4-pyrimidinediamine. LCMS: purity: 96%; MS (m/e): 438(MH⁺).

7.3.880 N4-(3-Chloro-4-methoxyphenyl)-5-fluoro-N2-[2-(methoxycarbonyl) benzofuran-5-yl]-2,4-pyrimidinediamine (R926950)

In a like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro -N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N4-(3-chloro-4-methoxyphenyl)-5-fluoro-4-pyrimidineamine and 5-amino-2-(methoxycarbonyl)benzofuran were reacted to produce N4-(3-chloro-4-methoxyphenyl)-5-fluoro-N2-[2-(methoxycarbonyl)benzofuran-5-yl]-2,4-pyrimidinediamine. ¹H NMR (DMSO-*d*₆): δ 9.34 (bs, 2H), 8.10-8.07 (m, 2H), 7.78 (t, 1H, J= 2.7 Hz), 7.66-7.53 (m, 4H), 7.12 (d, 1H, J= 9.3 Hz), 3.87 (s, 3H), 3.85 (s, 3H); LCMS: purity: 99%; MS (m/e): 443(MH⁺).

7.3.881 N4-(3-Chloro-4-methoxyphenyl)-5-fluoro-N2-[2,3-dihydro-2-(methoxycarbonyl)benzofuran-5-yl]-2,4-pyrimidinediamine (R926951)

In a like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N4-(3-chloro-4-methoxyphenyl)-5-fluoro-4-pyrimidineamine and 5-amino-2,3-dihydro-2-(methoxycarbonyl)benzofuran were reacted to produce N4-(3-chloro-4-methoxyphenyl)-5-fluoro-N2-[2,3-dihydro-2-(methoxycarbonyl)benzofuran-5-yl]-2,4-pyrimidinediamine. ¹H NMR (DMSO-*d*₆): δ 10.31

(bs, 1H), 10.04 (bs, 1H), 8.21 (d, 1H, J= 4.8 Hz), 7.75 (t, 1H, J= 3.0 Hz), 7.54 (td, 1H, J= 3.0 and 9.0 Hz), 7.34 (s, 1H), 7.20-7.15 (m, 2H), 6.80 (d, 1H, J= 8.1 Hz), 5.38-5.31 (m, 1H), 3.85 (s, 3H), 3.69 (s, 3H), 3.49 (dd, 1H, J= 11.1 and 16.5 Hz); LCMS: purity: 99%; MS (m/e): 446(MH⁺).

5 **7.3.882 N4-(3-Chloro-4-trifluoromethoxyphenyl)-5-fluoro-N2-[2,3-dihydro-2-(methoxycarbonyl)benzofuran-5-yl]-2,4-pyrimidinediamine (R926953)**

In a like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N4-(3-chloro-4-trifluoromethoxyphenyl)-5-fluoro-4-pyrimidineamine and 5-amino-2,3-dihydro-2-(methoxycarbonyl)benzofuran were reacted to produce N4-(3-chloro-4-trifluoromethoxyphenyl)-5-fluoro-N2-[2,3-dihydro-2-(methoxycarbonyl)benzofuran-5-yl]-2,4-pyrimidinediamine. ¹H NMR (DMSO-*d*₆): δ 9.99 (bs, 1H), 9.49 (bs, 1H), 8.18 (d, 1H, J= 4.5 Hz), 8.08 (t, 1H, J= 2.4 Hz), 7.81-7.74 (m, 1H), 7.49 (d, 1H, J= 8.1 Hz), 7.42 (s, 1H), 7.20 (d, 1H, J= 8.1 Hz), 6.78 (d, 1H, J= 8.7 Hz), 5.36 (m, 1H), 3.80-3.47 (m, 4H), 3.20 (dd, 1H, J= 6.0 and 16.5 Hz); LCMS: purity: 100%; MS (m/e): 500(MH⁺).

15 **7.3.883 N4-(3-Chloro-4-trifluoromethoxyphenyl)-5-fluoro-N2-[2,3-dihydro-2-[(N-methylamino)carbonyl]benzofuran-5-yl]-2,4-pyrimidinediamine (R926954)**

20 In a like manner to the preparation of N4-(3,5-dichloro-4-hydroxyphenyl)-5-fluoro-N2-[3-(N-morpholino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, 2-chloro-N4-(3-chloro-4-trifluoromethoxyphenyl)-5-fluoro-4-pyrimidineamine, methylamine hydrogen chloride salt, and diisopropylethylamine were reacted to provide N4-(3-chloro-4-trifluoromethoxyphenyl)-5-fluoro-N2-[2,3-dihydro-2-[(N-methylamino)carbonyl]benzofuran-5-yl]-2,4-pyrimidinediamine. ¹H NMR (DMSO-*d*₆): δ 9.59 (s, 1H), 9.10 (s, 2H), 8.13-8.10 (m, 1H), 8.08-7.98 (m, 1H), 7.82 (d, 1H, J= 8.1 Hz), 7.48-7.42 (m, 2H), 7.24 (d, 1H, J= 8.7 Hz), 6.72 (d, 1H, J= 8.7 Hz), 5.06 (dd, 1H, J= 5.4 and 9.3 Hz), 3.39 (dd, 1H, J= 10.5 and 15.6 Hz), 3.15 (dd, 1H, J= 6.3 and 15.9 Hz), 2.59 (d, 3H, J= 4.5 Hz); LCMS: purity: 95%; MS (m/e): 499(MH⁺).

7.3.884 N4-(3-Chloro-4-methoxyphenyl)-5-fluoro-N2-[2,3-dihydro-2-[(N-methylamino)carbonyl]benzofuran-5-yl]-2,4-pyrimidinediamine (R926955)

In a like manner to the preparation of N4-(3,5-dichloro-4-hydroxyphenyl)-5-fluoro-N2-[3-(N-morpholino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, 2-chloro-N4-(3-chloro-4-methoxyphenyl)-5-fluoro-4-pyrimidineamine, methylamine hydrochloride, and diisopropylethylamine were reacted to provide N4-(3-chloro-4-methoxyphenyl)-5-fluoro-N2-[2,3-dihydro-2-[(N-methylamino)carbonyl]benzofuran-5-yl]-2,4-pyrimidinediamine. ¹H NMR (DMSO-*d*₆): δ 9.24 (s, 1H), 8.99 (s, 2H), 8.02 (d, 1H, J= 3.0 Hz), 7.80-7.75 (m, 1H), 7.63 (d, 1H, J= 9.0 Hz), 7.47 (s, 1H), 7.23 (d, 1H, J= 8.1 Hz), 7.07 (d, 1H, J= 8.7 Hz), 6.69 (d, 1H, J= 8.1 Hz), 5.05 (dd, 1H, J= 2.1 and 9.9 Hz), 3.37 (dd, 1H, J= 10.5 and 15.9 Hz), 3.13 (dd, 1H, J= 6.0 and 15.9 Hz), 2.59 (d, 3H, J= 4.5 Hz); LCMS: purity: 95%; MS (m/e): 445(MH⁺).

7.3.885 5-Fluoro-N2-[2,3-dihydro-2-[(N-methylamino)carbonyl]benzofuran-5-yl]-N4-(4-isopropoxyphenyl)-2,4-pyrimidinediamine (R926956)

In a like manner to the preparation of N4-(3,5-dichloro-4-hydroxyphenyl)-5-fluoro-N2-[3-(N-morpholino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-(4-isopropoxyphenyl)-4-pyrimidineamine, methylamine hydrochloride, and diisopropylethylamine were reacted to provide 5-fluoro-N2-[2,3-dihydro-2-[(N-methylamino)carbonyl]benzofuran-5-yl]-N4-(4-isopropoxyphenyl)-2,4-pyrimidinediamine. ¹H NMR (DMSO-*d*₆): δ 9.11 (s, 1H), 8.92 (s, 1H), 8.06-7.98 (m, 1H), 7.97 (d, 1H, J= 4.2 Hz), 7.60-7.52 (m, 3H), 7.20 (d, 1H, J= 8.1 Hz), 6.85 (d, 2H, J= 8.7 Hz), 6.67 (d, 1H, J= 9.0 Hz), 5.04 (dd, 1H, J= 5.7 and 9.9 Hz), 4.56 (quintet, 1H, J= 6.6 Hz), 3.36 (dd, 1H, J= 10.5 and 16.5 Hz), 3.10 (dd, 1H, J= 5.7 and 15.3 Hz), 2.59 (d, 1H, J= 4.5 Hz), 1.24 (d, 6H, J= 6.6 Hz); LCMS: purity: 96%; MS (m/e): 438(MH⁺).

7.3.886 N2,N4-Bis(3-phenylphenyl)-2,4-pyrimidinediamine (R925809)

In a like manner to the preparation of N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, 2,4-dichloro-5-fluoropyrimidine and 3-aminobiphenyl were reacted to provide N2,N4-Bis(3-phenylphenyl)-2,4-pyrimidinediamine. LCMS: purity: 98%; MS (m/e): 415(MH⁺).

7.3.887 2-Dimethylamine-5-fluoro-N4-(thyrosinyl methyl ester) pyrimidine (R940110)

A solution of 2,4-dichloro-5-fluoropyrimidine (0.03 g, 0.18 mmol) and L-tyrosine methyl ester (0.14 g, 0.7 mmol) in DMF was heated at 100°C for 3 days. The reaction mixture was cooled to room temperature and diluted with H₂O (10 mL). Upon saturation with sodium chloride it was extracted with ethyl acetate (3 x 15 mL), dried over anhydrous sodium sulfate and the solvent was removed. The resulting residue was filtered through a pad of silica gel (200-400 mesh, hexanes/EtOAc 2/8) to obtain 2-dimethylamine-5-fluoro-N4-(thyrosinyl methyl ester) pyrimidine **R940110**. ¹H NMR (CDCl₃): δ 7.76 (1H, d, *J* = 3.2 Hz), 7.00 (2H, d, *J* = 7.5 Hz), 6.76 (2H, d, *J* = 7.5 Hz), 5.20 (1H, d, *J* = 7.5 Hz), 4.90 (1H, q, *J* = 5.0 Hz), 3.71 (3H, s), 3.14 (2H, m), 3.08 (6H, s); purity: 98%; MS (m/e): 335 (M+H).

7.3.888 5-Fluoro-N2-[3-(methylaminocarbonylmethyleneoxy)phenyl]-N4-(3-aminocarbonylphenyl)-2,4-pyrimidinediamine (R940299)

To a solution of 2-chloro-5-fluoro-N4-(3-aminocarbonylphenyl)-4-pyrimidineamine (0.050g, 0.18 mmol) in (2 mL) was added 3-(methylaminocarbonylmethyleneoxy)aniline (0.1g, 0.5 mmol). The mixture was heated in a sealed tube at 100 °C for 24h. The resulting reaction was diluted with H₂O (10 mL), acidified with 2N HCl (pH >2), saturated with sodium chloride and the resulting solid was filtered to give the desired product 5-fluoro-N2-[3-(methylaminocarbonylmethyleneoxy)phenyl]-N4-(3-aminocarbonylphenyl)-2,4-pyrimidinediamine **R940299**. Purification can be done by filtration through a pad of silica gel using 1-5% MeOH in CH₂Cl₂ or by crystallization using an appropriate solvent system. Alternatively, the reaction of equimolar amount of 2-chloro-5-fluoro-N4-(3-aminocarbonylphenyl)-4-pyrimidineamine and 3-(methylaminocarbonylmethyleneoxy)aniline in MeOH in a pressure tube at 110 °C for 24h or, in EtOH using microwave at 175 °C for 30-60 min followed by aqueous work up, also gave the desired product. ¹H NMR (DMSO-d₆): δ 9.79 (1H, s), 9.49 (1H, s), 8.26 (1H, d, *J* = 3.9 Hz), 8.15 (1H, t, *J* = 1.8 Hz), 8.10-8.02 (3H, m), 7.68 (1H, d, *J* = 7.5 Hz), 7.51 (1H, t, *J* = 7.9 Hz), 7.48 (1H, s), 7.38 (2H, m), 7.20 (1H, t, *J* = 8.4 Hz), 6.60 (1H, d, *J* = 9.3 Hz), 4.45 (2H, s), 2.74 (3H, d, *J* = 4.8 Hz); purity: 95 %; MS (m/e): 411 (MH+).

7.3.889 5-Fluoro-N2-[3-(methylaminocarbonylmethyleneoxy)phenyl]-N4-(3-methyloxycarbonyl-4-methoxyphenyl)-2,4-pyrimidinediamine (R940300)

In like manner to the preparation of 5-fluoro-N2-[3-

5 (methylaminocarbonylmethyleneoxy)phenyl]-N4-(3-aminocarbonylphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-(3-methyloxycarbonyl-4-methoxyphenyl)-4-pyrimidineamine and 3-(methylaminocarbonylmethyleneoxy)aniline were reacted to yield 5-fluoro-N2-[3-(methylaminocarbonylmethyleneoxy)phenyl]-N4-(3-methyloxycarbonyl-4-methoxyphenyl)-2,4-pyrimidinediamine **R940300**. ¹H NMR (DMSO-d₆): δ 9.66 (1H, s),
10 9.45 (1H, s), 8.21 (1H, d, *J* = 3.9 Hz), 8.06 (2H, m), 8.01 (1H, t, *J* = 2.7 Hz), 7.35 (2H, m), 7.23 (1H, d, *J* = 9 Hz), 7.18 (1H, t, *J* = 8.1 Hz), 6.60 (1H, d, *J* = 7.8 Hz), 4.45 (2H, s), 3.91 (3H, s), 3.84 (3H, s), 2.74 (3H, d, *J* = 3.6 Hz); purity: 93%; MS (m/e): 456 (MH⁺).

7.3.890 5-Fluoro-N4-(3-hydroxyphenyl)-N2-(3-methyloxycarbonyl-4-methoxyphenyl)-2,4-pyrimidinediamine (R940301)

15 In like manner to the preparation of 5-fluoro-N2-[3-

(methylaminocarbonylmethyleneoxy)phenyl]-N4-(3-aminocarbonylphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-(3-hydroxyphenyl)-4-pyrimidineamine and 3-methyloxycarbonyl-4-methoxyaniline were reacted to yield 5-fluoro-N4-(3-hydroxyphenyl)-N2-(3-methyloxycarbonyl-4-methoxyphenyl)-2,4-pyrimidinediamine **R940301**. ¹H NMR (DMSO-d₆): δ 9.93 (1H, s), 9.79 (1H, s), 9.54 (1H, s), 8.26 (1H, s, *J* = 4.5 Hz), 7.92 (1H, s), 7.81 (1H, dd, *J* = 9.3 Hz, *J* = 2.7 Hz), 7.32 (1H, d, *J* = 8.1 Hz), 7.20-7.13 (3H, m), 6.64 (1H, d, *J* = 8.1 Hz), 3.89 (3H, s), 3.84 (3H, s); purity: 97%; MS (m/e): 385 (MH⁺).

7.3.891 5-Fluoro-N4-(3-methylaminocarbonyl-4-methoxyphenyl)-N2-methyl-2,4-pyrimidinediamine (R940304)

25 A mixture of 2-chloro-5-fluoro-N4-(3-methyloxycarbonyl-4-methoxyphenyl)-4-pyrimidineamine (0.15 g, 0.4 mmol), methylamine hydrochloride (0.324 g, 48 mmol) and diisopropylethylamine (0.84 mL, 48 mmol) in MeOH (2 mL) was heated in a sealed tube at 100 °C for 24h (followed by TLC). The reaction was cooled to room temperature and
30 diluted with H₂O (20 mL). The solid was filtered, washed with H₂O and dried to obtain 5-fluoro-N4-(3-methylaminocarbonyl-4-methoxyphenyl)-N2-methyl-2,4-pyrimidinediamine **R940304**. ¹H NMR (DMSO-d₆): δ 10.65 (1H, s), 8.48 (1H, s), 8.29 (2H, m), 7.93 (1H, m),

7.28 (1H, d, $J = 9$ Hz), 4.00 (3H, s), 2.94 (3H, s), 2.90 (3H, d, $J = 4.5$ Hz) ; purity: 90% ; MS (m/e): 306 (MH⁺);

7.3.892 5-Fluoro-N2-[3-(methylaminocarbonylmethyleneoxy)phenyl]-N4-(3-methylaminocarbonyl-4-methoxyphenyl)-2,4-pyrimidinediamine (R940306)

In like manner to the preparation of 5-fluoro-N2-[3-(methylaminocarbonylmethyleneoxy)phenyl]-N4-(3-aminocarbonylphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-(3-methylaminocarbonyl-4-methoxyphenyl)-4-pyrimidineamine and 3-(methylaminocarbonylmethyleneoxy)aniline were reacted to yield 5-fluoro-N2-[3-(methylaminocarbonylmethyleneoxy)phenyl]-N4-(3-methylaminocarbonyl-4-methoxyphenyl)-2,4-pyrimidinediamine **R940306**. ¹H NMR (DMSO-d₆): δ 9.28 (1H, s), 9.21 (1H, s), 8.12 (1H, d, $J = 3.9$ Hz), 8.06 (1H, d, $J = 2.7$ Hz), 7.99 (1H, m), 7.89 (1H, dd, $J = 9.3$ Hz, $J = 2.7$ Hz), 7.52 (1H, q, $J = 4.9$ Hz), 7.41 (1H, t, $J = 2.1$ Hz), 7.37 (1H, d, $J = 7.5$ Hz), 7.10 (1H, t, $J = 8.1$ Hz), 6.83 (1H, d, $J = 9$ Hz), 6.53 (1H, dd, $J = 8.1$ Hz, $J = 1.8$ Hz), 4.40 (2H, s), 3.82 (3H, s), 2.96 (3H, d, $J = 5.1$ Hz), 2.73 (3H, d, $J = 4.5$ Hz) ; purity: 93% ; MS (m/e): 455 (MH⁺).

7.3.893 (R)-N2-[3-(dihydroxypropylaminocarbonylmethyleneoxy)phenyl]-5-fluoro-N4-(3-isopropylphenyl)-2,4-pyrimidinediamine (R940307)

In like manner to the preparation of 5-fluoro-N4-(3-methylaminocarbonyl-4-methoxyphenyl)-N2-methyl-2,4-pyrimidinediamine, 5-fluoro-N4-(3-isopropylphenyl)-N2-(3-methoxycarbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine and (R)-3-amino-1,2-propanediol were reacted to give (R)-N2-[3-(N-2,3-dihydroxypropylamino)carbonylmethyleneoxyphenyl]-5-fluoro-N4-(3-isopropylphenyl)-2,4-pyrimidinediamine **R940307**. ¹H NMR (DMSO-d₆): δ 9.96 (1H, s), 9.80 (1H, s), 8.29 (1H, d, $J = 4.5$ Hz), 7.98 (1H, t, $J = 5.5$ Hz), 7.77 (1H, d, $J = 7.2$ Hz), 7.57 (1H, s), 7.37 (1H, t, $J = 7.8$ Hz), 7.30-7.22 (3H, m), 7.12 (1H, d, $J = 7.8$ Hz), 6.70 (1H, d, $J = 7.5$ Hz), 4.47 (2H, s), 3.62 (1H, m), 3.38 (3H, m), 3.15 (1H, m), 2.94 (1H, quint, $J = 6.9$ Hz), 1.27 (6H, d, 6.9 Hz) ; purity: 99%; MS (m/e): 469 (M), 470 (MH⁺).

7.3.894 N4-(3-*tert*-Butylphenyl)-5-fluoro-N2-[3-(1,1-dimethyl-2-hydroxyethylaminocarbonylmethyleneoxy)-phenyl]-2,4-pyrimidinediamine (R940308)

In like manner to the preparation of 5-fluoro-N4-(3-methylaminocarbonyl-4-methoxyphenyl)-N2-methyl-2,4-pyrimidinediamine, N4-(3-*tert*-butylphenyl)-5-fluoro-N2-(3-methoxycarbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine and 2-amino-2-methyl-1-propanol were reacted to give N4-(3-*tert*-butylphenyl)-5-fluoro-N2-[3-(1,1-dimethyl-2-hydroxyethylaminocarbonylmethyleneoxy)-phenyl]-2,4-pyrimidinediamine **R940308**. ¹H NMR (DMSO-d₆): δ 9.38 (1H, s), 9.28 (1H, s), 8.20 (1H, d, *J* = 3.9 Hz), 7.99 (1H, d, *J* = 7.5 Hz), 7.60 (1H, t, *J* = 2.1 Hz), 7.46 (1H, s), 7.37 (2H, t, *J* = 7.9 Hz), 7.30 (1H, s), 7.19 (2H, t, *J* = 7.9 Hz), 6.56 (1H, dd, *J* = 7.5 Hz, *J* = 1.5 Hz), 5.06 (1H, t, *J* = 5.7 Hz), 4.37 (2H, s), 3.40 (2H, m), 1.36 (9H, s), 1.32 (6H, s) ; purity: 93% ; MS (m/e): 482 (MH⁺).

7.3.895 N4-(3-Aminomethylenephenyl)-5-fluoro-N2-[3-(methylaminocarbonylmethyleneoxy)phenyl]-2,4-pyrimidinediamine (R940309)

A mixture of N4-[3-(*N-tert*-butoxycarbonyl-*N*-aminomethylene)-phenyl]-2-chloro-5-fluoro-4-pyrimidineamine and 3-(methylaminocarbonylmethyleneoxy)aniline in MeOH was heated in a sealed tube at 100 °C for 12h. The reaction was cool to room temperature and the solvent was removed under reduce pressure. The resulting residue was filtered through a pad of silica gel (200-400 mesh, EtOAc/MeOH (2M NH₃) 95:5) to obtain the desired product N4-(3-aminomethylenephenyl)-5-fluoro-N2-[3-(methylaminocarbonylmethyleneoxy)phenyl]-2,4-pyrimidinediamine **R940309**. ¹H NMR (DMSO-d₆): δ 9.41 (1H, s), 9.23 (1H, s), 8.20 (1H, d, *J* = 3.9 Hz), 8.00 (1H, m), 7.78 (1H, s), 7.72 (1H, d, *J* = 7.2 Hz), 7.46 (1H, s), 7.42-7.33 (2H, m), 7.21 (1H, t, *J* = 7.8 Hz), 7.14 (1H, d, *J* = 7.8 Hz), 6.59 (1H, dd, *J* = 8.1 Hz, *J* = 2.4 Hz), 4.42 (2H, s), 3.79 (2H, s), 2.74 (3H, d, *J* = 4.8 Hz) ; purity: 98% ; MS (m/e): 397 (MH⁺).

7.3.896 N4-[3-(2-(N4-(3-aminomethylenephenyl)-5-fluoro-4-pyrimidineamine)-*N*-methylaminomethylene)-phenyl]-5-fluoro-N2-[3-(methylaminocarbonylmethyleneoxy)phenyl]-2,4-pyrimidineamine (R940311)

A mixture of N4-[3-(*N*-methylaminomethylene)-phenyl]-2-chloro-5-fluoro-4-pyrimidineamine (0.05 g, 0.18 mmol) and 3-(methylaminocarbonylmethyleneoxy)aniline (0.04 g, 0.22 mmol) in EtOH (0.5 mL), was heated at 175 °C for 35 min using microwave. An aqueous work up gave the desired N4-[3-(2-(N4-(3-aminomethylenephenyl)-5-fluoro-4-

pyrimidineamine)-N-methylaminomethylene)-phenyl]-5-fluoro-N2-[3-

(methylaminocarbonylmethyleneoxy)phenyl]-2,4-pyrimidineamine **R940311**. ¹H NMR

(DMSO-d₆): δ 9.48 (1H, s), 9.31 (1H, s), 9.26 (1H, s), 8.20 (1H, d, *J* = 3.6 Hz), 8.10-8.05

(4H, m), 7.62 (1H, s), 7.49 (2H, m), 7.41 (1H, t, *J* = 8.1 Hz), 7.36 (2H, m), 7.22 (1H, t, *J* =

8.4 Hz), 7.17 (1H, t, *J* = 8.4 Hz), 7.06 (1H, d, *J* = 7.5 Hz), 6.59 (1H, dd, *J* = 8.4 Hz, *J* = 2.4

Hz), 6.54 (1H, dd, *J* = 7.8 Hz, *J* = 2.4 Hz), 4.93 (2H, s), 4.46 (2H, s), 4.45 (2H, s), 3.28 (3H,

d, *J* = 3 Hz), 2.73 (6H, m) ; purity: 98%; MS (m/e) : 684 (M), 685 (MH⁺).

7.3.897 5-Fluoro-N2-[3-(methylaminocarbonylmethyleneoxy)phenyl]-N4-(3-*iso*-propylaminocarbonyl-4-methoxyphenyl)-2,4-pyrimidinediamine (R940312)

In like manner to the preparation of 5-fluoro-N2-[3-

(methylaminocarbonylmethyleneoxy)phenyl]-N4-(3-aminocarbonylphenyl)-2,4-

pyrimidinediamine, 2-chloro-5-fluoro-N4-(3- *N-iso*-propylaminomethylene-4-

methoxyphenyl)-4-pyrimidineamine and 3-(methylaminocarbonylmethyleneoxy)aniline

were reacted to produce 5-fluoro-N2-[3-(methylaminocarbonylmethyleneoxy)phenyl]-N4-

(3-*iso*-propylaminocarbonyl-4-methoxyphenyl)-2,4-pyrimidinediamine **R940312**. ¹H NMR

(DMSO-d₆): δ 10.09 (1H, s), 9.88 (1H, s), 8.25 (1H, d, *J* = 4.8 Hz), 8.07 (1H, d, *J* = 2.7 Hz),

8.05 (1H, m), 7.81 (1H, dd, *J* = 9 Hz, *J* = 2.7 Hz), 7.63 (1H, s), 7.25 (2H, m), 7.17 (1H, t, *J* =

8.25 Hz), 6.91 (1H, d, *J* = 9 Hz), 6.68 (1H, d, *J* = 8.1 Hz), 4.42 (2H, s), 3.85 (1H, m), 3.81

(3H, s), 2.72 (3H, d, *J* = 4.2 Hz), 1.30 (6H, d, *J* = 6 Hz) ; purity: 97% ; MS (m/e): 483

(MH⁺).

7.3.898 5-Fluoro-N2-[3-(methylaminocarbonylmethyleneoxy)phenyl]-N4-[3-(N-morpholinomethylene)-4-methoxyphenyl]-2,4-pyrimidinediamine (R940314)

In like manner to the preparation of 5-fluoro-N2-[3-

(methylaminocarbonylmethyleneoxy)phenyl]-N4-(3-aminocarbonylphenyl)-2,4-

pyrimidinediamine, N2-chloro-5-fluoro-N4-[3-(N-morpholinomethylene)-4-

methoxyphenyl]-4-pyrimidineamine and 3-(methylaminocarbonylmethyleneoxy)aniline

were reacted to produce 5-fluoro-N2-[3-(methylaminocarbonylmethyleneoxy)phenyl]-N4-

[3-(N-morpholinomethylene)-4-methoxyphenyl]-2,4-pyrimidinediamine **R940314**. ¹H NMR

(DMSO-d₆): δ 9.33 (1H, s), 9.21 (1H, s), 8.15 (1H, d, *J* = 3.6 Hz), 8.04 (1H, d, *J* = 4.8 Hz),

7.82 (1H, dd, *J* = 9 Hz, *J* = 2.7 Hz), 7.57 (1H, d, *J* = 3 Hz), 7.47 (1H, t, *J* = 1.95 Hz), 7.34

(1H, m), 7.18 (1H, t, *J* = 8.1 Hz), 7.04 (1H, d, *J* = 9 Hz), 6.56 (1H, dd, *J* = 8.4 Hz, *J* = 2.1

Hz), 4.40 (2H, s), 3.86 (3H, s), 3.63 (4H, t, $J = 4.5$ Hz), 3.53 (2H, s), 2.74 (3H, d, $J = 4.5$ Hz), 2.46 (4H, m) ; purity: 97%; MS (m/e): 497 (MH⁺).

7.3.899 N2-(3-Chloro-4-hydroxy-5-methylphenyl)-5-fluoro-N4-[3-(N-morpholinomethylene)-4-methoxyphenyl]-2,4-pyrimidinediamine (R940316)

In like manner to the preparation of 5-fluoro-N2-[3-(methylaminocarbonylmethyleneoxy)phenyl]-N4-(3-aminocarbonylphenyl)-2,4-pyrimidinediamine, N2-chloro-5-fluoro-N4-[3-(N-morpholinomethylene)-4-methoxyphenyl]-4-pyrimidineamine and 4-amino-2-chloro-6-methylphenol were reacted to produce N2-(3-chloro-4-hydroxy-5-methylphenyl)-5-fluoro-N4-[3-(N-morpholinomethylene)-4-methoxyphenyl]-2,4-pyrimidinediamine R940316. ¹H NMR (DMSO-d₆): δ 9.28 (1H, s), 9.01 (1H, s), 8.65 (1H, s), 8.11 (1H, d, $J = 3.9$ Hz), 7.76 (1H, dd, $J = 9$ Hz, $J = 3$ Hz), 7.61 (1H, d, $J = 2.4$ Hz), 7.50 (1H, d, $J = 2.7$ Hz), 7.30 (1H, d, $J = 2.1$ Hz), 7.04 (1H, d, $J = 8.7$ Hz), 3.87 (3H, s), 3.63 (4H, t, $J = 4.3$ Hz), 3.52 (2H, s), 2.45 (4H, m), 2.17 (3H, s) ; purity: 97% ; MS (m/e): 474 (MH⁺).

7.3.900 N4-(3-N-methylaminomethylenephenyl)-5-fluoro-N2-[3-(methylaminocarbonylmethyleneoxy)phenyl]-2,4-pyrimidinediamine (R940317)

In like manner to the preparation of 5-fluoro-N2-[3-(methylaminocarbonylmethyleneoxy)phenyl]-N4-(3-aminocarbonylphenyl)-2,4-pyrimidinediamine, N4-[3-(N-*tert*-butoxycarbonyl-N-methylaminomethylene)-phenyl]-2-chloro-5-fluoro-4-pyrimidineamine and 3-(methylaminocarbonylmethyleneoxy)aniline were reacted to produce N4-(3-N-methylaminomethylenephenyl)-5-fluoro-N2-[3-(methylaminocarbonylmethyleneoxy)phenyl]-2,4-pyrimidinediamine R940317. ¹H NMR (DMSO-d₆): δ 9.41 (1H, s), 9.31 (1H, s), 9.29 (1H, s), 8.20 (1H, d, $J = 3$ Hz), 8.05 (1H, m), 7.80 (1H, d, $J = 7.8$ Hz), 7.74 (1H, s), 7.45-7.35 (3H, m), 7.21 (1H, t, $J = 8.1$ Hz), 7.13 (1H, d, $J = 7.5$ Hz), 6.59 (1H, d, $J = 9.6$ Hz), 4.43 (2H, s), 3.71 (2H, s), 2.75 (3H, d, $J = 4.2$ Hz), 2.35 (3H, s) ; purity: 83.9% ; MS (m/e): 411 (MH⁺).

7.3.901 N2-(3-Chloro-4-hydroxy-5-methylphenyl)-5-fluoro-N4-[3-(N-piperazinomethylene)-4-methoxyphenyl]-2,4-pyrimidinediamine (R940318)

In like manner to the preparation of 5-fluoro-N2-[3-(methylaminocarbonylmethyleneoxy)phenyl]-N4-(3-aminocarbonylphenyl)-2,4-

pyrimidinediamine, N4-[3-(N-piperazinomethylene)-4-methoxyphenyl]-2-chloro-5-fluoro-4-pyrimidineamine and 4-amino-2-chloro-6-methylphenol were reacted to produce N2-(3-chloro-4-hydroxy-5-methylphenyl)-5-fluoro-N4-[3-(N-piperazinomethylene)-4-methoxyphenyl]-2,4-pyrimidinediamine **R940318**. ¹H NMR (DMSO-d₆): δ 9.27 (1H, s), 9.00 (1H, s), 8.10 (1H, d, *J* = 3.6 Hz), 7.75 (1H, dd, *J* = 8.7 Hz, *J* = 2.7 Hz), 7.61 (1H, d, *J* = 2.4 Hz), 7.49 (1H, d, *J* = 2.4 Hz), 7.31 (1H, d, *J* = 2.4 Hz), 7.03 (1H, d, *J* = 9 Hz), 3.86 (3H, s), 3.49 (2H, s), 2.75 (4H, t, *J* = 4.65 Hz), 2.39 (4H, m), 2.17 (3H, s) ; purity: 95%; MS (m/e): 473 (MH⁺).

7.3.902 N4-(3-(N-*tert*-Butoxycarbonyl-N-*iso*-propylaminomethylene)-4-methoxyphenyl)-5-fluoro-N2-[3-(methylaminocarbonylmethyleneoxy)phenyl]-2,4-pyrimidinediamine (R940319)

In like manner to the preparation of 5-fluoro-N2-[3-(methylaminocarbonylmethyleneoxy)phenyl]-N4-(3-aminocarbonylphenyl)-2,4-pyrimidinediamine, N4-(3-(N-*tert*-butoxycarbonyl-N-*iso*-propylaminomethylene)-4-methoxyphenyl)-2-chloro-5-fluoro-4-pyrimidineamine and 3-(methylaminocarbonylmethyleneoxy)aniline were reacted to produce N4-(3-(N-*tert*-butoxycarbonyl-N-*iso*-propylaminomethylene)-4-methoxyphenyl)-5-fluoro-N2-[3-(methylaminocarbonylmethyleneoxy)phenyl]-2,4-pyrimidinediamine **R940319**. ¹H NMR (DMSO-d₆): δ 9.44 (1H, s), 8.95 (1H, s), 8.15 (1H, d, *J* = 3.6 Hz), 8.06 (1H, m), 7.83 (1H, m), 7.74 (1H, m), 7.56 (1H, m), 7.37 (1H, m), 7.20 (1H, t, *J* = 7.9 Hz), 7.02 (1H, d, *J* = 9.3 Hz), 6.57 (1H, d, *J* = 7.8 Hz), 4.44 (2H, s), 4.42 (1H, m), 4.33 (2H, s), 3.89 (3H, s), 2.74 (3H, d, *J* = 4.8 Hz), 1.52-1.30 (9H, m), 1.16 (6H, d, *J* = 6.9 Hz) ; purity: 98% ; MS (m/e): 569 (MH⁺).

7.3.903 N4-(3-N,N-Dimethylaminomethylene-4-methoxyphenyl)-5-fluoro-N2-[3-(methylaminocarbonylmethyleneoxy)phenyl]-2,4-pyrimidinediamine (R940321)

In like manner to the preparation of 5-fluoro-N2-[3-(methylaminocarbonylmethyleneoxy)phenyl]-N4-(3-aminocarbonylphenyl)-2,4-pyrimidinediamine, 2-chloro-N4-(3-N,N-dimethylaminomethylene-4-methoxyphenyl)-5-fluoro-4-pyrimidineamine and 3-(methylaminocarbonylmethyleneoxy)aniline were reacted to produce N4-(3-N,N-dimethylaminomethylene-4-methoxyphenyl)-5-fluoro-N2-[3-(methylaminocarbonylmethyleneoxy)phenyl]-2,4-pyrimidinediamine **R940321**.

¹H NMR (DMSO-d₆): δ 9.32 (1H, s), 9.23 (1H, s), 8.14 (1H, d, *J* = 3.9 Hz), 8.05 (1H, m), 7.83 (1H, dd, *J* = 8.7 Hz, *J* = 2.4 Hz), 7.55 (1H, d, *J* = 2.4 Hz), 7.45 (1H, s), 7.36 (1H, d, *J* = 8.4 Hz), 7.18 (1H, t, *J* = 8.1 Hz), 7.03 (1H, d, *J* = 9 Hz), 6.56 (1H, dd, *J* = 7.2 Hz, *J* = 1.5 Hz), 4.41 (2H, s), 3.86 (3H, s), 2.73 (3H, d, *J* = 4.5 Hz), 2.24 (6H, s) ; purity: 91.8% ;
 5 MS (m/e): 455 (MH⁺).

7.3.904 N4-[(2,2-Dimethyl-4H-benzo[1,4]oxazin-3-one)-6-yl]-5-fluoro-N2-[3-(methylaminocarbonylmethyleneoxy)phenyl]-2,4-pyrimidinediamine (R940323)

In like manner to the preparation of 5-fluoro-N2-[3-(methylaminocarbonylmethyleneoxy)phenyl]-N4-(3-aminocarbonylphenyl)-2,4-pyrimidinediamine, 2-chloro-N4-[(2,2-dimethyl-4H-benzo[1,4]oxazin-3-one)-6-yl]-5-fluoro-4-pyrimidineamine and 3-(methylaminocarbonylmethyleneoxy)aniline were reacted to produce N4-[(2,2-dimethyl-4H-benzo[1,4]oxazin-3-one)-6-yl]-5-fluoro-N2-[3-(methylaminocarbonylmethyleneoxy)phenyl]-2,4-pyrimidinediamine **R940323**.

¹H NMR (DMSO-d₆): δ 10.70 (1H, s), 9.45 (1H, s), 9.19 (1H, s), 8.17 (1H, d, *J* = 3.9 Hz), 8.05 (1H, m), 7.43-7.34 (4H, m), 7.17 (1H, t, *J* = 8.25 Hz), 6.98 (1H, d, *J* = 8.4 Hz), 6.56 (1H, dd, *J* = 7.8 Hz, *J* = 2.1 Hz), 4.25 (2H, s), 2.74 (3H, d, *J* = 4.5 Hz), 1.5 (6H, s) ;
 15 purity: 98.7% ; MS (m/e): 467 (MH⁺).

7.3.905 N4-[3-Dihydro-2,2-dimethyl-4-(2-pyridyl)-benzo[1,4]oxazin-6-yl]-5-fluoro-N2-[3-(methylaminocarbonylmethyleneoxy)phenyl]-2,4-pyrimidinediamine (R940337)

In like manner to the preparation of 5-fluoro-N2-[3-(methylaminocarbonylmethyleneoxy)phenyl]-N4-(3-aminocarbonylphenyl)-2,4-pyrimidinediamine, 2-chloro-N4-[3-dihydro-2,2-dimethyl-4-(2-pyridyl)-benzo[1,4]oxazin-6-yl]-5-fluoro-4-pyrimidineamine and 3-(methylaminocarbonylmethyleneoxy)aniline were reacted to produce N4-[3-dihydro-2,2-dimethyl-4-(2-pyridyl)-benzo[1,4]oxazin-6-yl]-5-fluoro-N2-[3-(methylaminocarbonylmethyleneoxy)phenyl]-2,4-pyrimidinediamine

R940337. ¹H NMR (DMSO-d₆): δ 9.28 (1H, s), 9.20 (1H, s), 8.34 (1H, dd, *J* = 4.8 Hz, *J* = 1.2 Hz), 8.14 (1H, d, *J* = 3.8 Hz), 8.03 (1H, m), 7.64-7.60 (2H, m), 7.51-7.46 (3H, m), 7.37 (1H, d, *J* = 8.4 Hz), 7.17 (1H, t, *J* = 8.1 Hz), 6.94-6.91 (2H, m), 6.55 (1H, dd, *J* = 8.4 Hz, *J* = 3Hz), 4.42 (2H, s), 3.93 (2H, s), 2.74 (3H, d, *J* = 4.5 Hz), 1.32 (6H, s) ; purity: 98.2% ; MS (m/e): 530 (MH⁺);

7.3.906 N4-[(2,2-Dimethyl-4H-benzo[1,4]oxazin-3-one)-6-yl]-5-fluoro-N2-(1-methylindazolin-5-yl)-2,4-pyrimidinediamine (R940338)

In like manner to the preparation of 5-fluoro-N2-[3-

5 (methylaminocarbonylmethyleneoxy)phenyl]-N4-(3-aminocarbonylphenyl)-2,4-pyrimidinediamine, 2-chloro-N4-[(2,2-dimethyl-4H-benzo[1,4]oxazin-3-one)-6-yl]-5-fluoro-4-pyrimidineamine and 5-amino-1-methyl-1-indazole were reacted to produce N4-[(2,2-dimethyl-4H-benzo[1,4]oxazin-3-one)-6-yl]-5-fluoro-N2-(1-methylindazolin-5-yl)-2,4-pyrimidinediamine **R940338**. ¹H NMR (DMSO-d₆): δ 10.73 (1H, s), 9.39 (1H, s), 9.17 (1H, s), 8.21 (1H, s), 8.16 (1H, d, *J* = 3.9 Hz), 7.87 (1H, s), 7.56 (2H, m), 7.41 (1H, m), 7.32 (1H, s), 7.00 (1H, d, *J* = 8.4 Hz), 4.07 (3H, s), 1.51 (6H, s); purity: 99.2%; MS (m/e): 434 (MH⁺).

7.3.907 N4-[(2,2-Difluoro-4H-benzo[1,4]oxazin-3-one)-6-yl]-5-fluoro-N2-[3-(methylaminocarbonylmethyleneoxy)phenyl]-2,4-pyrimidinediamine (R921303)

In like manner to the preparation of 5-fluoro-N2-[3-

15 (methylaminocarbonylmethyleneoxy)phenyl]-N4-(3-aminocarbonylphenyl)-2,4-pyrimidinediamine, 2-chloro-N4-[(2,2-difluoro-4H-benzo[1,4]oxazin-3-one)-6-yl]-5-fluoro-4-pyrimidineamine and 3-(methylaminocarbonylmethyleneoxy)aniline were reacted to produce N4-[(2,2-difluoro-4H-benzo[1,4]oxazin-3-one)-6-yl]-5-fluoro-N2-[3-(methylaminocarbonylmethyleneoxy)phenyl]-2,4-pyrimidinediamine **R921303**. ¹H NMR (DMSO-d₆): δ 12.05 (1H, s), 9.67 (1H, s), 9.27 (1H, s), 8.24 (1H, d, *J* = 3.6 Hz), 8.05 (1H, m), 7.73-7.68 (1H, m), 7.56 (1H, t, *J* = 2.7 Hz), 7.50 (1H, s), 7.36 (2H, d, *J* = 8.7 Hz), 7.19 (1H, t, *J* = 8.2 Hz), 6.58 (1H, dd, *J* = 8.4 Hz, *J* = 2.4 Hz), 4.34 (2H, s), 2.74 (3H, d, *J* = 4.5 Hz); ¹⁹F NMR (DMSO-d₆): δ -21643, -46385; purity: 100%; MS (m/e): 475 (MH⁺).

7.3.908 N4-[(2,2-Dimethyl-4H-5-pyrido[1,4]oxazin-3-one)-7-yl]-5-fluoro-N2-[3-(methylaminocarbonylmethyleneoxy)phenyl]-2,4-pyrimidinediamine (R940345)

In like manner to the preparation of 5-fluoro-N2-[3-

30 (methylaminocarbonylmethyleneoxy)phenyl]-N4-(3-aminocarbonylphenyl)-2,4-pyrimidinediamine, 2-chloro-N4-[(2,2-dimethyl-4H-5-pyrido[1,4]oxazin-3-one)-7-yl]-5-fluoro-4-pyrimidineamine and 3-(methylaminocarbonylmethyleneoxy)aniline were reacted to produce N4-[(2,2-dimethyl-4H-5-pyrido[1,4]oxazin-3-one)-7-yl]-5-fluoro-N2-[3-

(methylaminocarbonylmethyleneoxy)phenyl]-2,4-pyrimidinediamine **R940345**. ¹H NMR (DMSO-d₆): δ 11.23 (1H, s), 9.69 (1H, s), 9.54 (1H, s), 8.50 (1H, s), 8.25 (1H, d, *J*= 3.3 Hz), 8.06 (1H, m), 7.96 (1H, t, *J*= 2.5 Hz), 7.41-7.36 (2H, m), 7.24 (1H, t, *J*= 8.25 Hz), 6.34 (1H, d, *J*= 8.7 Hz), 4.47 (2H, s), 2.74 (3H, d, *J*= 3.3 Hz), 1.53 (6H, s) ; purity: 98.4% ;
5 MS (m/e): 468 (MH⁺).

7.3.909 N4-[(2,2-Dimethyl-4H-benzo[1,4]oxazin-3-one)-6-yl]-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine (R940346)

In like manner to the preparation of 5-fluoro-N2-[3-(methylaminocarbonylmethyleneoxy)phenyl]-N4-(3-aminocarbonylphenyl)-2,4-pyrimidinediamine, 2-chloro-N4-[(2,2-dimethyl-4H-benzo[1,4]oxazin-3-one)-6-yl]-5-fluoro-4-pyrimidineamine and 3-aminophenol were reacted to produce N4-[(2,2-dimethyl-4H-benzo[1,4]oxazin-3-one)-6-yl]-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine **R940346**. ¹H NMR (DMSO-d₆): δ 10.75 (1H, s), 8.25 (1H, d, *J*= 4.5 Hz), 7.42-7.37 (1H, m), 7.34 (1H, s), 7.10 (3H, m), 7.00 (1H, d, *J*= 8.4 Hz), 6.53 (1H, m), 1.50 (6H, s) ; purity:
15 97.5% ; MS (m/e): 396 (MH⁺).

7.3.910 N4-[(2,2-Dimethyl-4H-5-pyrido[1,4]oxazin-3-one)-6-yl]-5-fluoro-N2-[3-(methylaminocarbonylmethyleneoxy)phenyl]-2,4-pyrimidinediamine (R940347)

In like manner to the preparation of 5-fluoro-N2-[3-(methylaminocarbonylmethyleneoxy)phenyl]-N4-(3-aminocarbonylphenyl)-2,4-pyrimidinediamine, 2-chloro-N4-[(2,2-dimethyl-4H-5-pyrido[1,4]oxazin-3-one)-6-yl]-5-fluoro-4-pyrimidineamine and 3-(methylaminocarbonylmethyleneoxy)aniline were reacted to produce N4-[(2,2-dimethyl-4H-5-pyrido[1,4]oxazin-3-one)-6-yl]-5-fluoro-N2-[3-(methylaminocarbonylmethyleneoxy)phenyl]-2,4-pyrimidinediamine **R940347**. ¹H NMR (DMSO-d₆): δ 11.20 (1H, s), 9.46 (1H, s), 8.26 (1H, d, *J*= 3.6 Hz), 8.06 (1H, s), 7.71 (1H, m), 7.49 (1H, d, *J*= 8.4 Hz), 7.45 (1H, s), 7.38 (1H, d, *J*= 9 Hz), 7.21 (1H, t, *J*= 8.1 Hz), 6.61 (1H, d, *J*= 8.7 Hz), 4.47 (2H, s), 2.74 (3H, s), 1.52 (6H, s); purity: 100% ; MS (m/e):
25 468 (MH⁺).

7.3.911 N4-[3-Dihydro-2,2-dimethyl-4-(2-pyridyl)-benzo[1,4]oxazin-6-yl]-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine (R940348)

In like manner to the preparation of 5-fluoro-N2-[3-(methylaminocarbonylmethyleneoxy)phenyl]-N4-(3-aminocarbonylphenyl)-2,4-

pyrimidinediamine, 2-chloro-N4-[3-dihydro-2,2-dimethyl-4-(2-pyridyl)-benzo[1,4]oxazin-6-yl]-5-fluoro-4-pyrimidineamine and 3-aminophenol were reacted to produce N4-[3-dihydro-2,2-dimethyl-4-(2-pyridyl)-benzo[1,4]oxazin-6-yl]-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine **R940348**. ¹H NMR (DMSO-d₆): δ 9.25 (1H, s), 9.23 (1H, s), 9.02 (1H, s), 8.34 (1H, d, *J* = 4.5 Hz), 8.11 (1H, d, *J* = 3.3 Hz), 7.62 (2H, m), 7.52 (2H, m), 7.22 (1H, s), 7.19 (1H, d, *J* = 7.5 Hz), 7.03 (1H, t, *J* = 7.9 Hz), 6.93 (2H, m), 6.38 (1H, d, *J* = 7.8 Hz), 3.93 (2H, s), 1.32 (6H, s) ; purity: 96.5%.

7.3.912 N4-[(2,2-Difluoro-4H-benzo[1,4]oxazin-3-one)-6-yl]-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine (R940349)

In like manner to the preparation of 5-fluoro-N2-[3-(methylaminocarbonylmethyleneoxy)phenyl]-N4-(3-aminocarbonylphenyl)-2,4-pyrimidinediamine, 2-chloro-N4-[(2,2-difluoro-4H-benzo[1,4]oxazin-3-one)-6-yl]-5-fluoro-4-pyrimidineamine and 3-aminophenol were reacted to produce N4-[(2,2-difluoro-4H-benzo[1,4]oxazin-3-one)-6-yl]-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine **R940349**. ¹H NMR (DMSO-d₆): δ 12.03 (1H, s), 9.63 (1H, s), 9.26 (1H, s), 9.09 (1H, s), 8.21 (1H, d, *J* = 3.6 Hz), 7.70 (1H, dd, *J* = 9 Hz, *J* = 2.4 Hz), 7.59 (1H, d, *J* = 2.7 Hz), 7.34 (1H, d, *J* = 9.3 Hz), 7.26 (1H, s), 7.16 (1H, d, *J* = 7.8 Hz), 7.04 (1H, t, *J* = 8.2 Hz), 6.41 (1H, d, *J* = 10.2 Hz) ; ¹⁹F NMR (DMSO-d₆): δ -21646, -46516 ; purity: 95.8% ; MS (m/e): 404 (MH⁺);

7.3.913 N2,N4-[(2,2-Dimethyl-4H-benzo[1,4]oxazin-3-one)-6-yl]-5-fluoro-2,4-pyrimidinediamine (R940350)

In like manner to the preparation of 5-fluoro-N2-[3-(methylaminocarbonylmethyleneoxy)phenyl]-N4-(3-aminocarbonylphenyl)-2,4-pyrimidinediamine, 2-chloro-N4-[(2,2-dimethyl-4H-5-benzo[1,4]oxazin-3-one)-6-yl]-5-fluoro-4-pyrimidineamine and 6-amino-2,2-dimethyl-4H-benzo[1,4]oxazin-3-one were reacted to produce N2,N4-[(2,2-dimethyl-4H-benzo[1,4]oxazin-3-one)-6-yl]-5-fluoro-2,4-pyrimidinediamine **R940350**. ¹H NMR (DMSO-d₆): δ 10.68 (1H, s), 10.62 (1H, s), 9.38 (1H, s), 9.04 (1H, s), 8.11 (1H, d, *J* = 3.6 Hz), 7.46 (1H, dd, *J* = 8.1 Hz, *J* = 1.8 Hz), 7.33-7.26 (3H, m), 6.95 (1H, d, *J* = 8.7 Hz), 6.84 (1H, d, *J* = 8.4 Hz), 1.49 (6H, s), 1.45 (6H, s) ; purity: 95.4% ; MS (m/e): 479 (MH⁺).

7.3.914 N2-[(2,2-Difluoro-4H-benzo[1,4]oxazin-3-one)-6-yl]-N4-[(2,2-dimethyl-4H-benzo[1,4]oxazin-3-one)-6-yl]-5-fluoro-2,4-pyrimidinediamine (R940351)

In like manner to the preparation of 5-fluoro-N2-[3-

(methylaminocarbonylmethyleneoxy)phenyl]-N4-(3-aminocarbonylphenyl)-2,4-pyrimidinediamine, 2-chloro-N4-[(2,2-dimethyl-4H-5-pyrido[1,4]oxazin-3-one)-6-yl]-5-fluoro-4-pyrimidineamine and 6-amino-2,2-difluoro-4H-benzo[1,4]oxazin-3-one were reacted to produce N2-[(2,2-difluoro-4H-benzo[1,4]oxazin-3-one)-6-yl]-N4-[(2,2-dimethyl-4H-benzo[1,4]oxazin-3-one)-6-yl]-5-fluoro-2,4-pyrimidinediamine **R940351**. ¹H NMR (DMSO-d₆): δ 11.99 (1H, s), 10.74 (1H, s), 9.64 (1H, s), 9.50 (1H, s), 8.19 (1H, d, *J* = 3.9 Hz), 7.50 (2H, m), 7.43 (1H, dd, *J* = 8.4 Hz, *J* = 1.8 Hz), 7.32 (1H, s), 7.20 (1H, d, *J* = 9.3 Hz), 6.98 (1H, d, *J* = 8.7 Hz), 1.49 (6H, s); purity: 94.77%; MS (m/e): 487 (MH⁺).

7.3.915 N2,N4-[(2,2-Difluoro-4H-benzo[1,4]oxazin-3-one)-6-yl]-5-fluoro-2,4-pyrimidinediamine (R940352)

In like manner to the preparation of 5-fluoro-N2-[3-

(methylaminocarbonylmethyleneoxy)phenyl]-N4-(3-aminocarbonylphenyl)-2,4-pyrimidinediamine, 2-chloro-N4-[(2,2-difluoro-4H-benzo[1,4]oxazin-3-one)-6-yl]-5-fluoro-4-pyrimidineamine and 6-amino-2,2-difluoro-4H-benzo[1,4]oxazin-3-one were reacted to produce N2,N4-[(2,2-difluoro-4H-benzo[1,4]oxazin-3-one)-6-yl]-5-fluoro-2,4-pyrimidinediamine **R940352**. ¹H NMR (DMSO-d₆): δ 12.08 (1H, s), 12.00 (1H, s), 9.72 (1H, s), 9.44 (1H, s), 8.23 (1H, d, *J* = 3.6 Hz), 7.73 (1H, dd, *J* = 11.1 Hz, *J* = 1.5 Hz), 7.6 (1H, s), 7.56 (1H, s), 7.51 (1H, dd, *J* = 9.6 Hz, *J* = 2.4 Hz), 7.35 (1H, d, *J* = 9 Hz), 7.24 (1H, d, *J* = 8.7 Hz); ¹⁹F NMR (DMSO-d₆): δ -21670, -21722, -4651; purity: 100%; MS (m/e): 495 (MH⁺).

7.3.916 N4-[(2,2-Difluoro-4H-benzo[1,4]oxazin-3-one)-6-yl]-5-fluoro-N2-(2-methoxycarbonylbenzofur-5-yl)-2,4-pyrimidinediamine (R940353)

In like manner to the preparation of 5-fluoro-N2-[3-

(methylaminocarbonylmethyleneoxy)phenyl]-N4-(3-aminocarbonylphenyl)-2,4-pyrimidinediamine, 2-chloro-N4-[(2,2-difluoro-4H-benzo[1,4]oxazin-3-one)-6-yl]-5-fluoro-4-pyrimidineamine and methyl 5-aminobenzofuran-2-carboxylate were reacted to produce N4-[(2,2-difluoro-4H-benzo[1,4]oxazin-3-one)-6-yl]-5-fluoro-N2-(2-methoxycarbonylbenzofur-5-yl)-2,4-pyrimidinediamine **R940353**. ¹H NMR (DMSO-d₆):

δ 12.05 (1H, s), 9.69 (1H, s), 9.43 (1H, s), 8.28 (1H, s), 8.25 (1H, d, J = 3.6 Hz), 7.40-7.64 (4H, m), 7.54 (1H, s), 7.38 (1H, d, J = 9 Hz), 3.97 (3H, s) ; ^{19}F NMR (DMSO- d_6): δ -21707, -46489 ; purity: 97.77% ; MS (m/e): 486 (MH $^+$).

5 **7.3.917 N4-[(2,2-Dimethyl-4H-benzo[1,4]oxazin-3-one)-6-yl]-5-fluoro-N2-(2-methoxycarbonylbenzofur-5-yl)-2,4-pyrimidinediamine (R940354)**

In like manner to the preparation of 5-fluoro-N2-[3-(methylaminocarbonylmethyleneoxy)phenyl]-N4-(3-aminocarbonylphenyl)-2,4-pyrimidinediamine, 2-chloro-N4-[(2,2-dimethyl-4H-benzo[1,4]oxazin-3-one)-6-yl]-5-fluoro-4-pyrimidineamine and methyl 5-aminobenzofuran-2-carboxylate were reacted to produce N4-[(2,2-dimethyl-4H-benzo[1,4]oxazin-3-one)-6-yl]-5-fluoro-N2-(2-methoxycarbonylbenzofur-5-yl)-2,4-pyrimidinediamine **R940354**. ^1H NMR (DMSO- d_6): δ 10.75 (1H, s), 9.67 (1H, s), 9.53 (1H, s), 8.25 (1H, s), 8.21 (1H, d, J = 4.2 Hz), 7.66 (2H, s), 7.59 (1H, s), 7.31 (1H, d, J = 8.7 Hz), 7.26 (1H, s), 7.03 (1H, d, J = 8.1 Hz), 3.97 (3H, s), 1.52 (6H, s) ; purity: 95.58% ; MS (m/e): 478 (MH $^+$).

7.3.918 N2,N4-Bis(3-N-acetylaminophenyl)-5-fluoro-N2,N4-pyrimidinediacetylamine (R950244)

N2,N4-Bis(3-aminophenyl)-5-fluoro-2,4-pyrimidinediamine, dimethylaminopyridine (DMAP) and acetic anhydride were refluxed in pyridine for 1 hour. The mixture was cooled to room temperature, concentrated, and the residue was subjected to column chromatography on silica gel (CHCl_3 :Acetone, 2:1) to give N2,N4-bis(3-N-acetylaminophenyl)-5-fluoro-N2,N4-pyrimidinediacetylamine. ^1H NMR (MeOD, 300 MHz): δ 8.65 (d, 1H, J = 2.4 Hz), 7.15-7.58 (m, 8H), 2.24 (s, 3H), 2.22 (s, 3H), 2.14 (s, 3H), 2.09 (s, 3H); LCMS: ret. time: 17.03 min.; purity: 87.0%; MS (m/e): 478.89 (MH $^+$).

25 **7.3.919 N4-(3-N,N-Diacetylaminophenyl)-N2-(3-N-acetylaminophenyl)-5-fluoro-N2,N4-pyrimidinediacetylamine (R950245)**

N2,N4-Bis(3-aminophenyl)-5-fluoro-2,4-pyrimidinediamine, dimethylaminopyridine (DMAP) and acetic anhydride were refluxed in pyridine for 1 hour. The mixture was cooled to room temperature, concentrated, and the residue was subjected to column chromatography on silica gel (CHCl_3 :Acetone, 2:1) to give N4-(3-N,N-diacetylaminophenyl)-N2-(3-N-acetylaminophenyl)-5-fluoro-N2,N4-

pyrimidinediacetylamine. ^1H NMR (MeOD, 300 MHz): δ 8.65 (d, 1H, $J = 2.4$ Hz), 7.03-7.66 (m, 8H), 2.21 (s, 6H), 2.14 (s, 3H), 2.12 (s, 3H), 2.08 (s, 3H); LCMS: ret. time: 19.27 min.; purity: 92.6%; MS (m/e): 521.01 (MH^+).

5 **7.3.920 N4-(3-N-Acetylaminophenyl)-N2-(3-N,N-diacetylaminophenyl)-5-fluoro-N2,N4-pyrimidinediacetylamine (R950246)**

N2,N4-Bis(3-aminophenyl)-5-fluoro-2,4-pyrimidinediamine, dimethylaminopyridine (DMAP) and acetic anhydride were refluxed in pyridine for 1 hour. The mixture was cooled to room temperature, concentrated, and the residue was subjected to column chromatography on silica gel (CHCl_3 :Acetone, 2:1) to give N4-[3-N-acetylaminophenyl]-N2-(3-N,N-diacetylaminophenyl)-5-fluoro-N2,N4-pyrimidinediacetylamine. ^1H NMR (MeOD, 300 MHz): δ 8.66 (d, 1H, $J = 2.4$ Hz), 6.88-7.57 (m, 8H), 2.22 (s, 6H), 2.11 (s, 3H), 2.10 (s, 3H), 2.09 (s, 3H); LCMS: ret. time: 18.89 min.; purity: 83.0%; MS (m/e): 520.97 (MH^+).

15 **7.3.921 N2,N4-Bis(3-N,N-diacetylaminophenyl)-5-fluoro-N2,N4-pyrimidinediacetylamine (R950247)**

N2,N4-Bis(3-aminophenyl)-5-fluoro-2,4-pyrimidinediamine, dimethylaminopyridine (DMAP) and acetic anhydride were refluxed in pyridine for 1 hour. The mixture was cooled to room temperature, concentrated, and the residue was subjected to column chromatography on silica gel (CHCl_3 :Acetone, 2:1) to give N2,N4-bis(3-N,N-diacetylaminophenyl)-5-fluoro-N2,N4-pyrimidinediacetylamine. ^1H NMR (MeOD, 300 MHz): δ 8.58 (d, 1H, $J = 2.4$ Hz), 6.75-7.53 (m, 8H), 2.04 (s, 3H), 2.03 (s, 3H), 2.01 (s, 6H), 1.99 (s, 6H); LCMS: ret. time: 21.51 min.; purity: 91.8%; MS (m/e): 563.00 (MH^+).

25 **7.3.922 N4-(3-Nitrophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R950261)**

A mixture of equimolar amounts of 2-chloro-N4-(3-nitrophenyl)-5-fluoro-4-aminopyridine and 3-(N-methylamino)carbonylmethyleneoxyaniline in MeOH in a pressure tube at 110°C for 24h or in EtOH using microwave at 175°C for 10-20 min followed by aqueous work up gave N4-(3-nitrophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. LCMS: purity: 92.7%; MS (m/e): 412.94 (MH^+).

7.3.923 N4-(3-Aminophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine HCl salt (R950262)

N4-(3-Nitrophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine and Pd/C 10% (50% water content) were suspended in EtOH-10% aqueous HCl (1 : 1) and hydrogenated in a Parr apparatus for 2 hours (22 °C, 50 psi). The suspension was filtered over celite and carefully washed with MeOH. The combined filtrates were concentrated under reduced pressure to give the HCl salt of N4-(3-aminophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine as a white solid. LCMS: purity: 92.7%; MS (m/e): 383.07 (M-Cl⁺, 100).

7.3.924 N4-(3-Aminophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R950263)

The HCl salt of N4-(3-aminophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine was neutralized with aqueous sodium carbonate solution and extracted with EtOAc. The organic phase was dried and concentrated to give N4-(3-aminophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine as a pale yellow solid. ¹H NMR (DMSO): δ 10.00 (s, 1H), 9.92 (s, 1H), 8.07 (d, 1H, J = 2.4 Hz), 8.15 (bs, 2H), 7.91-8.07 (m, 3H), 7.08-7.21 (m, 5H), 6.56 (d, 1H, J = 7.2 Hz), 4.32 (s, 2H), 2.72 (d, 3H, J = 4.8 Hz); LCMS: purity: 92.7%; MS (m/e): 383.17 (MH⁺, 100).

7.3.925 N4-(3-Bis-N-methylaminophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R950264)

A solution of N4-(3-aminophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine in DME-DMF (1 : 1) was treated with 10 equivalents of MeI and sodium bicarbonate. The mixture was stirred for 1.5 hours at 70°C and purified by flash chromatography on silica gel to give N4-(3-bis-N-methylaminophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine as a white solid. LCMS: purity: 90.2%; MS (m/e): 411.04 (MH⁺, 100).

7.3.926 N4-(3-N-Hydroxyethylaminophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R950265)

A solution of N4-(3-aminophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine in DME-DMF (1 : 1) was treated with 10 equivalents of 2-bromoethanol and sodium bicarbonate. The mixture was stirred for 16 hours at 70°C and purified by flash chromatography on silica gel to give N4-(3-N-hydroxyethylaminophenyl)-5-fluoro. LCMS: purity: 90.2%; MS (m/e): 427.33 (MH⁺, 100).

7.3.927 N4-(3-Bis(N-hydroxyethyl)aminophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R950266)

A solution of N4-(3-aminophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine in DME-DMF (1 : 1) was treated with 10 equivalents of 2-bromoethanol and sodium bicarbonate. The mixture was stirred for 16 hours at 70°C and purified by flash chromatography on silica gel to give N4-(3-bis(N-hydroxyethyl)aminophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine as a white solid. LCMS: purity: 94.2%; MS (m/e): 471.46 (MH⁺, 100).

7.3.928 N4-(3-N-Methylaminophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R950267)

A solution of N4-(3-aminophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine in DME-DMF (1 : 1) was treated with 10 equivalents of MeI and sodium bicarbonate. The mixture was stirred for 1.5 hours at 70°C and purified by flash chromatography on silica gel to give N4-(3-N-methylaminophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine as a white solid. LCMS: purity: 92.3%; MS (m/e): 397.02 (MH⁺, 100).

7.3.929 N4-(3-Carboxy-4-hydroxyphenyl)-5-fluoro-N2-[3-ethoxycarbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R950290)

A mixture of equimolar amounts of 2-chloro-N4-(3-carboxy-4-hydroxyphenyl)-5-fluoro-4-aminopyridine and 3-ethoxycarbonylmethyleneoxyaniline in MeOH in a pressure

tube at 110°C for 24h or in EtOH using microwave at 175°C for 10-20 min followed by aqueous work up gave N4-(3-carboxy-4-hydroxyphenyl)-5-fluoro-N2-[3-ethoxycarbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. LCMS: purity: 97.8%; MS (m/e): 443.20 (MH⁺).

5 **7.3.930 N4-(3-Carboxy-4-hydroxyphenyl)-5-fluoro-N2-[3-carboxymethyleneoxyphenyl]-2,4-pyrimidinediamine (R950291)**

10 The reaction of N4-(3-carboxy-4-hydroxyphenyl)-5-fluoro-N2-[3-ethoxycarbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (0.1 g) and LiOH (10 equivalents) in MeOH:water (1:1, v/v) for 1h at room temperature followed by treatment with aqueous HCl gave the solid. The resulting solid was filtered, washed with water and dried to give N4-(3-carboxy-4-hydroxyphenyl)-5-fluoro-N2-[3-carboxymethyleneoxyphenyl]-2,4-pyrimidinediamine. LCMS: purity: 91.5%; MS (m/e): 415.16 (MH⁺).

15 **7.3.931 N4-(3-Methoxycarbonyl-4-hydroxyphenyl)-5-fluoro-N2-[3-ethoxycarbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R950293)**

20 A solution of N4-(3-carboxy-4-hydroxyphenyl)-5-fluoro-N2-[3-ethoxycarbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine in dry MeOH was treated with a 4 M solution of HCl in dioxane. The mixture was stirred for 1 hour at 22°C, concentrated to dryness and purified by flash chromatography on silica gel to give N4-(3-methoxycarbonyl-4-hydroxyphenyl)-5-fluoro-N2-[3-ethoxycarbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine as a white solid. LCMS: purity: 96.8%; MS (m/e): 457.25 (MH⁺).

25 **7.3.932 N4-(4-Methoxy-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-ethoxycarbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R950294)**

30 A mixture of equimolar amounts of 2-chloro-N4-(4-methoxy-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-4-aminopyridine and 3-ethoxycarbonylmethyleneoxyaniline in EtOH using microwave at 175°C for 10-20 min followed by aqueous work up gave N4-(4-methoxy-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-ethoxycarbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. LCMS: purity: 92.1%; MS (m/e): 469.26 (MH⁺).

7.3.933 N4-(4-Methoxy-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-methoxycarbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R950295)

A mixture of equimolar amounts of 2-chloro-N4-(4-methoxy-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-4-aminopyridine and 3-ethoxycarbonylmethyleneoxyaniline in MeOH in a pressure tube at 110°C for 24h followed by aqueous work up gave N4-(4-methoxy-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-methoxycarbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. LCMS: purity: 87.6%; MS (m/e): 455.26 (MH⁺).

7.3.934 N4-(4-Ethoxy-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R950296)

A solution of N4-(4-ethoxy-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-ethoxycarbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine in EtOH was treated with the HCl salt of methylamine. The mixture was stirred for 4 hours at 100°C, concentrated to dryness and purified by flash chromatography on silica gel to give N4-(4-ethoxy-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine as a white solid. LCMS: purity: 87.4%; MS (m/e): 468.29 (MH⁺).

7.3.935 N4-(4-Carboxyethyleneoxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R950344)

A mixture of equimolar amounts of 2-chloro-N4-(4-carboxyethyleneoxyphenyl)-5-fluoro-4-aminopyridine and 3-(N-methylamino)carbonylmethyleneoxyaniline in MeOH in a pressure tube at 110°C for 24h or in EtOH using microwave at 175°C for 10-20 min followed by aqueous work up gave N4-(4-carboxyethyleneoxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. LCMS: purity: 97.8%; MS (m/e): 456.32 (MH⁺).

7.3.936 N4-(2,3-Dihydro-4-benzopyranon-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R950345)

A solution of N4-(4-Methoxycarbonylethyleneoxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine in TfoH was heated

for 2 hours at 100°C. Aqueous work up followed by flash chromatography on silica gel gave N4-(2,3-dihydro-4-benzopyranon-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine as a white solid. LCMS: purity: 92.2%; MS (m/e): 435.95 (MH⁺).

5 **7.3.937 N4-(4-Methoxycarbonylethyleneoxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R950346)**

10 A solution of N4-(4-carboxyethyleneoxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine in dry MeOH was treated with a 4 M solution of HCl in dioxane. The mixture was stirred for 1 hour at 22°C, concentrated to dryness and purified by flash chromatography on silica gel to give N4-(4-methoxycarbonylethyleneoxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine as a white solid. LCMS: purity: 85.2%; MS (m/e): 468.01 (MH⁺).

15 **7.3.938 N4-(4-Hydroxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R950347)**

20 The reaction of N4-(4-methoxycarbonylethyleneoxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine and LiOH (10 equivalents) in MeOH:water (1:1, v/v) for 1h at room temperature followed by treatment with aqueous HCl gave a pale yellow solid. The resulting solid was filtered, washed with water and dried to give N4-(4-hydroxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. LCMS: purity: 94.7%; MS (m/e): 382.03 (MH⁺).

25 **7.3.939 N4-(2,3-Dihydro-4-oxime-benzopyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R950348)**

30 A mixture N4-(2,3-dihydro-4-benzopyranon-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine and hydroxylamine (20 equivalents) in pyridine at 22°C for 16 hours followed by aqueous work up gave N4-(2,3-dihydro-4-oxime-benzopyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine as a white solid. LCMS: purity: 89.5%; MS (m/e): 451.00 (MH⁺).

7.3.940 N4-(4-Hydroxy-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R950349)

A solution of N4-(2,3-dihydro-4-benzopyranon-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine in dry MeOH was treated with a sodiumcyanoborohydride. The mixture was stirred for 1 hour at 22°C, concentrated to dryness and purified by flash chromatography on silica gel to give N4-(4-Hydroxy-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine as a white solid. ¹H NMR (DMSO): δ 9.19 (s, 1H), 9.09 (s, 1H), 8.03 (d, 1H, J = 2.4 Hz), 7.28-7.93 (m, 5H), 7.07 (t, 1H, J = 7.2 Hz), 6.71 (d, 1H, J = 7.2 Hz), 6.44 (dd, 1H, J = 2.6, 7.2 Hz), 5.31 (d, 1H, J = 5.1 Hz), 4.14-4.59 (m, 3H), 4.30 (s, 2H), 2.63 (d, 3H, J = 4.8 Hz), 1.82-2.03 (m, 2H); LCMS: purity: 93.3%; MS (m/e): 440.15 (MH⁺).

7.3.941 N4-(2,3-Dihydro-4-O-methyloxime-benzopyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R950356)

A mixture N4-(2,3-dihydro-4-benzopyranon-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine and methoxyamine (20 equivalents) in pyridine at 22°C for 16 hours followed by aqueous work up gave N4-(2,3-dihydro-4-oxime-benzopyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine as a white solid. LCMS: purity: 85.5%; MS (m/e): 465.10 (MH⁺).

7.3.942 N4-(4-Amino-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R950368)

A mixture N4-(4-azido-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine and Pd/C (10%) in MeOH was hydrogenated at 22°C for 6 hours (40psi). The mixture was filtered and concentrated to dryness to give N4-(4-amino-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine as a white solid. ¹H NMR (DMSO): δ 9.60 (s, 1H), 9.46 (s, 1H), 8.73 (bs, 3H), 8.00-8.10 (m, 3H), 7.47 (s, 1H), 7.42 (m, 1H), 7.29 (d, 1H, J = 7.2 Hz), 7.11 (t, 1H, J = 7.2 Hz), 6.82 (d, 1H, J 7.0 Hz), 6.46 (m, 1H), 4.23-4.46 (m, 3H), 4.31 (s, 3H), 2.63 (d, 3H, J = 4.8 Hz), 2.09-2.29 (m, 2H); LCMS: purity: 97.6%; MS (m/e): 438.98 (MH⁺).

7.3.943 N4-(3-Methylcarbonylphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R950371)

A mixture of equimolar amounts of 2-chloro-N4-(3-methylcarbonylphenyl)-5-fluoro-4-aminopyridine and 3-(N-methylamino)carbonylmethyleneoxyaniline in MeOH in a pressure tube at 110°C for 24h or in EtOH using microwave at 175°C for 10-20 min followed by aqueous work up gave N4-(3-methylcarbonylphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine as a white solid. ¹H NMR (DMSO): δ 10.16 (s, 1H), 9.82 (s, 1H), 8.24 (d, 1H, J = 2.4 Hz), 8.15 (s, 1H), 7.91-8.07 (m, 2H), 7.70 (d, 1H, J = 7.0 Hz), 7.49 (t, 1H, J = 7.2 Hz), 7.08-7.21 (m, 3H), 6.56 (d, 1H, J = 7.2 Hz), 4.30 (s, 3H), 2.62 (d, 3H, J = 4.8 Hz), 2.48 (s, 3H); LCMS: purity: 93.8%; MS (m/e): 410.50 (MH⁺).

7.3.944 N4-(3-Phenylcarbonylphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R950372)

A mixture of equimolar amounts of 2-chloro-N4-(3-phenylcarbonylphenyl)-5-fluoro-4-aminopyridine and 3-(N-methylamino)carbonylmethyleneoxyaniline in MeOH in a pressure tube at 110°C for 24h or in EtOH using microwave at 175°C for 10-20 min followed by aqueous work up gave N4-(3-phenylcarbonylphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine as a white solid. LCMS: purity: 86.0%; MS (m/e): 472.50 (MH⁺).

7.3.945 N4-(3-Methylcarbonyloximephenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R950373)

A mixture N4-(3-methylcarbonylphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine and hydroxylamine (20 equivalents) in pyridine at 22°C for 16 hours followed by aqueous work up gave N4-(3-methylcarbonyloximephenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine as a white solid. ¹H NMR (DMSO): δ 11.21 (s, 1H), 10.11 (s, 1H), 9.85 (s, 1H), 6.54-8.23 (m, 9H), 4.32 (s, 2H), 2.63 (d, J = 7.0 Hz, 3H), 2.47 (s, 3H); LCMS: purity: 92.4%; MS (m/e): 425.28 (MH⁺).

7.3.946 N4-(3-Phenylcarbonyloximephenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R950374)

A mixture N4-(3-phenylcarbonylphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine and hydroxylamine (20 equivalents) in pyridine at 22°C for 16 hours followed by aqueous work up gave N4-(3-phenylcarbonyloximephenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine as a white solid. ¹H NMR (DMSO): δ 11.63 (s, 1H), 10.30 (s, 1H), 9.85 (s, 1H), 6.44-8.43 (m, 14H), 4.42 (s, 2H), 2.63 (d, J = 7.0 Hz, 3H); LCMS: purity: 92.4%; MS (m/e): 487.31 (MH⁺).

7.3.947 N2,N4-Bis(3-methylcarbonylphenyl)-5-fluoro-2,4-pyrimidinediamine (R950376)

A mixture of 2,4-dichloro-5-fluoropyridine and three equivalents of 3-acetophenone in MeOH in a pressure tube at 110°C for 24h or in EtOH using microwave at 175°C for 10-20 min followed by aqueous work up gave N2,N4-bis(3-methylcarbonylphenyl)-5-fluoro-2,4-pyrimidinediamine as a white solid. LCMS: purity: 93.1%; MS (m/e): 365.19 (MH⁺).

7.3.948 N2,N4-Bis(3-phenylcarbonylphenyl)-5-fluoro-2,4-pyrimidinediamine (R950377)

A mixture of 2,4-dichloro-5-fluoropyridine and three equivalents of 3-benzophenone in MeOH in a pressure tube at 110°C for 24h or in EtOH using microwave at 175°C for 10-20 min followed by aqueous work up gave N2,N4-bis(3-phenylcarbonylphenyl)-5-fluoro-2,4-pyrimidinediamine as a white solid. LCMS: purity: 95.7%; MS (m/e): 489.29 (MH⁺).

7.3.949 N2,N4-Bis(2,3-dihydro-4-benzopyranon-6-yl)-5-fluoro-2,4-pyrimidinediamine (R950378)

A solution of N2,N4-bis(4-methoxycarbonylethyleneoxyphenyl)-5-fluoro-2,4-pyrimidinediamine in TfOH was heated for 2 hours at 100°C. Aqueous work up followed by flash chromatography on silica gel gave N2,N4-bis(2,3-dihydro-4-benzopyranon-6-yl)-5-fluoro-2,4-pyrimidinediamine as a white solid. ¹H NMR (DMSO): δ 9.36 (s, 1H), 9.14 (s, 1H), 8.06 (d, 1H, J = 2.4 Hz), 7.72-7.99 (m, 3H), 6.97 (d, J = 7.2 Hz, 1H), 6.87 (d, J = 7.2 Hz, 1H), 4.42-4.52 (m, 4H), 2.70-2.78 (m, 4H); LCMS: purity: 94.3%; MS (m/e): 484.50 (MH⁺).

7.3.950 N2,N4-Bis(3-methylcarbonyloximephenyl)-5-fluoro-2,4-pyrimidinediamine (R950379)

A mixture of N2,N4-bis(3-methylcarbonylphenyl)-5-fluoro-2,4-pyrimidinediamine and hydroxylamine (20 equivalents) in pyridine at 22°C for 16 hours followed by aqueous work up gave N2,N4-bis(3-methylcarbonyloximephenyl)-5-fluoro-2,4-pyrimidinediamine as a white solid. ¹H NMR (DMSO): δ 11.21 (s, 1H), 10.11 (s, 1H), 9.85 (s, 1H), 6.54-8.23 (m, 9H), 4.32 (s, 2H), 2.63 (d, J = 7.0 Hz, 3H), 2.47 (s, 3H); LCMS: purity: 92.1%; MS (m/e): 393.06 (M-H⁺).

7.3.951 N2,N4-Bis(3-phenylcarbonyloximephenyl)-5-fluoro-2,4-pyrimidinediamine (R950380)

A mixture of N2,N4-bis(3-phenylcarbonylphenyl)-5-fluoro-2,4-pyrimidinediamine and hydroxylamine (20 equivalents) in pyridine at 22°C for 16 hours followed by aqueous work up gave N2,N4-bis(3-phenylcarbonyloximephenyl)-5-fluoro-2,4-pyrimidinediamine as a white solid. LCMS: purity: 93.3%; MS (m/e): 486.05 (M-H⁺).

7.3.952 N2,N4-Bis(2,3-dihydro-4-oxime-benzopyran-6-yl)-5-fluoro-2,4-pyrimidinediamine (R950381)

A mixture of N2,N4-bis(2,3-dihydro-4-benzopyranon-6-yl)-5-fluoro-2,4-pyrimidinediamine and hydroxylamine (20 equivalents) in pyridine at 22°C for 16 hours followed by aqueous work up gave N2,N4-bis(2,3-dihydro-4-oxime-benzopyran-6-yl)-5-fluoro-2,4-pyrimidinediamine as a white solid. LCMS: purity: 98.1%; MS (m/e): 449.03 (M-H⁺).

7.3.953 N4-(4-Acetyloxy-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R950382)

A solution of N4-(4-hydroxy-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine in pyridine was treated with acetic anhydride at 22°C for 16 hours. Aqueous work up gave N4-(4-acetyloxy-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine as a white solid. ¹H NMR (DMSO): δ 10.43 (bs, 1H), 9.62 (bs, 1H), 8.03 (d, 1H, J = 2.4 Hz), 7.10-7.83 (m, 7H), 6.83 (d, 1H, J = 7.4 Hz), 6.52 (d, 1H, J = 7.2 Hz), 5.01 (m, 1H), 4.75 (s, 2H), 4.03-4.32 (m, 2H), 2.62 (s, 3H), 2.23 (s, 3H), 1.93-2.13 (m, 2H); LCMS: purity: 92.1%; MS (m/e): 393.06 (M-H⁺).

7.3.954 N4-(4-Azido-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R950383)

A solution of N4-(4-hydroxy-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine in dry THF was treated with 2 equivalents of DPPA and DBU. The mixture was stirred for 3 hours at 22°C, concentrated to dryness and purified by flash chromatography on silica gel to give N4-(4-azido-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine as a white solid. ¹H NMR (DMSO): δ 10.09 (bs, 1H), 9.83 (bs, 1H), 8.18 (d, 1H, J = 2.4 Hz), 7.97 (m, 1H), 7.11-7.61 (m, 6H), 6.82 (d, 1H, J = 7.8 Hz), 6.62 (d, 1H, J = 7.2 Hz), 4.78 (s, 2H), 4.03-4.33 (m, 3H), 2.62 (s, 3H), 1.93-2.13 (m, 2H); LCMS: purity: 97.9%; MS (m/e): 463.07 (MH⁺).

7.3.955 N4-(4-Benzopyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R950385)

A solution of N4-(4-hydroxy-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine in THF was treated with boron trifluoride etherate at 80°C for 8 hours. Aqueous work up gave N4-(4-benzopyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine as a white solid. ¹H NMR (DMSO): δ 9.18 (s, 1H), 9.14 (s, 1H), 8.03 (d, J = 2.4 Hz, 1H), 7.93 (bs, 1H), 5.86-7.48 (m, 9H), 4.73-4.74 (m, 2H), 4.33 (s, 2H), 2.62 (s, 3H); LCMS: purity: 96.5%; MS (m/e): 420.07 (M-H⁺).

7.3.956 N4-(3-Hydroxymethylen-4-methoxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R950386)

A mixture of equimolar amounts of 2-chloro-N4-(3-hydroxymethylen-4-methoxyphenyl)-5-fluoro-4-aminopyridine and 3-(N-methylamino)carbonylmethyleneoxyaniline in MeOH in a pressure tube at 110°C for 24h or in EtOH using microwave at 175°C for 10-20 min followed by aqueous work up gave N4-(3-hydroxymethylen-4-methoxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine as a white solid. LCMS: purity: 89.2%; MS (m/e): 410.5 (MH⁺).

7.3.957 N4-(3-Amino-4-ethoxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R950388)

A mixture of 2-chloro-N4-(3-amino-4-ethoxyphenyl)-5-fluoro-4-aminopyridine and 3 equivalents of 3-(N-methylamino)carbonylmethyleneoxyaniline in MeOH in a pressure tube at 110°C for 24h or in EtOH using microwave at 175°C for 10-20 min followed by aqueous work up gave N4-(3-amino-4-ethoxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine as a white solid. LCMS: purity: 95.1%; MS (m/e): 427.18 (MH⁺).

7.3.958 N4-(4-Ethoxy-3-hydroxysulfonylphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R950389)

A solution of N4-(4-hydroxy-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine in HOAc was treated with sodium nitrate followed by addition of concentrated aqueous HCl and copper dichloride. The mixture was stirred for 2 hours at 22°C for 8 hours and purified by aqueous work up followed by column chromatography on silica gel to give N4-(4-ethoxy-3-hydroxysulfonylphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. LCMS: purity: 82.3%; MS (m/e): 474.09 (M-H⁺).

7.3.959 N2,N4-Bis(3-methoxycarbonyl-4-trifluoromethoxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R950391)

A mixture of 2,4-dichloro-5-fluoropyridine and three equivalents of 3-methoxycarbonyl-4-trifluoromethoxyaniline in MeOH in a pressure tube at 110°C for 24h or in EtOH using microwave at 175°C for 10-20 min followed by aqueous work up N2,N4-bis(3-methoxycarbonyl-4-trifluoromethoxyphenyl)-5-fluoro-2,4-pyrimidinediamine as a white solid. ¹H NMR (DMSO): δ 9.96 (s, 1H), 9.82 (s, 1H), 8.16-8.26 (m, 4H), 7.91 (dd, 1H, J = 3.0, 7.2 Hz), 7.42 (d, 1H, J = 7.2 Hz), 7.31 (d, 1H, J = 7.2 Hz), 3.77 (s, 3H), 3.75 (s, 3H); LCMS: purity: 93.0%; MS (m/e): 565.37 (MH⁺).

7.3.960 N4-(3-Methoxycarbonyl-4-trifluoromethoxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R950392)

A mixture of equimolar amounts of 2-chloro-N4-(3-methoxycarbonyl-4-trifluoromethoxyphenyl)-5-fluoro-4-aminopyridine and 3-(N-

methylamino)carbonylmethyleneoxyaniline in MeOH in a pressure tube at 110°C for 24h or in EtOH using microwave at 175°C for 10-20 min followed by aqueous work up gave N4-(3-methoxycarbonyl-4-trifluoromethoxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine as a white solid.

5 LCMS: purity: 95.8%; MS (m/e): 510.41 (MH⁺).

7.3.961 N4-(4-Acetylamino-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R950393)

A solution of N4-(4-hydroxy-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine in dry MeCN was
10 treated with concentrated sulfuric acid. The mixture was stirred for 3 hours at 22°C, concentrated to dryness and purified by flash chromatography on silica gel to give N4-(4-acetylamino-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine as a white solid. ¹H
15 NMR (DMSO): δ 10.46 (bs, 1H), 9.52 (bs, 1H), 7.98 (d, 1H, J = 2.4 Hz), 7.12-7.73 (m, 7H), 6.66 (d, 1H, J = 7.2 Hz), 6.49 (d, 1H, J = 7.2 Hz), 4.75 (s, 2H), 4.03-4.32 (m, 2H), 3.80 (m, 1H), 2.64 (s, 3H), 2.143 (s, 3H), 1.90-2.11 (m, 2H); LCMS: purity: 92.1%; MS (m/e): 393.06 (M-H⁺). LCMS: purity: 96.2%; MS (m/e): 479.13 (M-H⁺).

7.3.962 N4-[2,4-Dihydro-1-oxo-4H-imidazo[2,1-c][1,4]benzoxazin-8-yl]-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine (R945236)

N4-[2H-1,4-Benzoxazin-3(4H)-one-6-yl]-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine (800 mg, 2.18 mmol) and phosphorus pentasulfide (800 mg, 1.80 mmol) were stirred in pyridine (5 mL) at 70 °C for 2h. The reaction solution was treated with 1N
25 HCl solution to pH 5. The precipitation was collected with filtration, washed with water, dried to give N4-[2H-1,4-benzoxazin-3(4H)-thione-6-yl]-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine.

N4-[2H-1,4-Benzoxazin-3(4H)-thione-6-yl]-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine (400 mg, 1.04 mmol), glycine (500 mg) and triethylamine (0.5 mL) were stirred in methanol (10 mL) at 70 °C overnight. The undissolved salt was filtered off,
30 washed with methanol. The filtrate was evaporated and redissolved in THF (5mL) and DMF (5 mL). To the solution were added EDC (200 mg), HOAt (200 mg) and diisopropylethylamine (0.2 mL). The reaction solution was stirred at 70 °C for 0.5 h. The

mixture was diluted with ethyl acetate (60 mL) and washed with water (2 x 60 mL). The organic layer was separated, dried, evaporated and purified by flash column chromatography (EtOAc/hexanes = 1:1, EtOAc) to give N4-[2,4-dihydro-1-oxo-4H-imidazo[2,1-c][1,4]benzoxazin-8-yl]-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine as a white solid. ¹H NMR (CDCl₃): δ 4.35 (t, J= 2.1 Hz, 2H), 4.92 (t, J= 2.1 Hz, 2H), 6.44 (dd, J= 1.5 and 8.1 Hz, 1H), 6.81 (m, 2H), 6.99 (s, 1H), 7.11 (m, 2H), 7.39 (m, 2H), 7.97 (d, J= 3.0 Hz, 1H), 8.02 (s, 1H), 8.57 (d, J= 2.4 Hz, 1H); ¹⁹F NMR (282 MHz, CDCl₃): δ - 167.46; LCMS: ret. time: 13.71 min.; purity: 93.18%; MS (m/e): 407.10 (MH⁺).

7.3.963 5-Fluoro-N2-(3-hydroxyphenyl)-N4-[1-oxo-1,2,3,6-tetrahydropyrimido[2,1-c][1,4]benzoxazin-9-yl]-2,4-pyrimidinediamine (R945237)

In a manner analogous to the preparation of N4-[2,4-dihydro-1-oxo-4H-imidazo[2,1-c][1,4]benzoxazin-8-yl]-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, N4-[2H-1,4-benzoxazin-3(4H)-thione-6-yl]-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine (400 mg, 1.04 mmol) and β-alanine (500 mg) gave 5-fluoro-N2-(3-hydroxyphenyl)-N4-[1-oxo-1,2,3,6-tetrahydropyrimido[2,1-c][1,4]benzoxazin-9-yl]-2,4-pyrimidinediamine as a white solid. ¹H NMR (acetone-d₆): δ 2.68 (t, J= 7.2 Hz, 2H), 3.71 (t, J= 7.2 Hz, 2H), 4.62 (t, J= 1.2 Hz, 2H), 6.42 (ddd, J= 1.2 and 2.4 and 7.5 Hz, 1H), 6.98-7.08 (m, 3H), 7.38 (t, J= 2.4 Hz, 1H), 7.62 (dd, J= 2.4 and 8.7 Hz, 1H), 7.96 (d, J= 3.3 Hz, 1H), 8.12 (s, 1H), 8.16 (s, 1H), 8.52 (d, J= 2.7 Hz, 1H), 8.65 (s, 1H); ¹⁹F NMR (282 MHz, acetone-d₆): δ - 168.04.

7.3.964 5-Fluoro-N2-(3-methylaminocarbonylmethylenoxyphenyl)-N4-[2H-pyrido[3,2-b]-1,4-oxazin-3(4H)-one-7-yl]-2,4-pyrimidinediamine (R945242)

2H-Pyrido[3,2-b]-1,4-oxazin-3(4H)-one (500 mg) was treated with nitric acid (5 mL) and sulfuric acid (5 mL). The reaction mixture was heated to 70 °C for 30 min and then poured into ice-water. The solution was neutralized with sodium bicarbonate to pH 6. The yellow precipitation was collected by filtration, washed with water and dried to give a mixture of nitrated products (regio-isomers).

The mixture of nitrated compounds was reduced under hydrogenolysis conditions using 10% Pd-C in methanol at 40 psi for 30 min. The catalyst was filtered off. The filtrate was evaporated and treated with 2,4-dichloro-5-fluoropyrimidine (200 mg) in methanol (5

mL), water (5 mL). The reaction mixture was heated at 70 °C overnight, then evaporated. The residue was reacted with 3-methylaminocarbonylmethyleneoxyaniline (300 mg) in methanol (5 mL) and water (1 mL) at 100 °C overnight. The reaction mixture was diluted with 1N HCl solution (60 mL). The brown precipitation was collected by filtration, washed
 5 with water and dried to give 5-fluoro-N2-(3-methylaminocarbonylmethyleneoxyphenyl)-N4-[2H-pyrido[3,2-b]-1,4-oxazin-3(4H)-one-7-yl]-2,4-pyrimidinediamine. ¹H NMR (DMSO-d₆): δ 2.62 (d, J= 4.8 Hz, 3H), 4.33 (s, 2H), 4.63 (s, 2H), 6.48 (dd, J= 2.4 and 7.5 Hz, 1H), 7.11 (t, J= 8.1 Hz, 1H), 7.27 (d, J= 7.8 Hz, 1H), 7.36 (s, 1H), 7.86 (d, J= 2.1 Hz, 1H), 7.97 (m, 1H), 8.12 (d, J= 3.6 Hz, 1H), 8.38 (d, J= 2.1 Hz, 1H), 9.33 (s, 1H), 9.46 (s,
 10 1H), 11.18 (s, 1H); ¹⁹F NMR (282 MHz, DMSO-d₆): δ - 164.49; LCMS: ret. time: 13.16 min.; purity: 79.30%; MS (m/e): 440.16 (MH⁺).

7.3.965 5-Fluoro-N2-(3-methylaminocarbonylmethyleneoxyphenyl)-N4-[2H-pyrido[3,2-b]-1,4-oxazin-7-yl]-2,4-pyrimidinediamine (R945263)

2H-Pyrido[3,2-b]-1,4-oxazin-3(4H)-one (1g, 6.66 mmol) was refluxed with boron
 15 hydride methyl sulfide complex (2 mL) in THF (10 mL) for 30 min to give 2H-pyrido[3,2-b]-1,4-oxazine. In a manner analogous to the preparation of 5-fluoro-N2-(3-methylaminocarbonylmethyleneoxyphenyl)-N4-[2H-pyrido[3,2-b]-1,4-oxazin-3(4H)-one-7-yl]-2,4-pyrimidinediamine, 2H-pyrido[3,2-b]-1,4-oxazine was nitrated, reduced and reacted
 20 with 2,4-dichloro-5-fluoropyrimidine (400 mg) and 3-methylaminocarbonylmethyleneoxyaniline (500 mg) to give 5-fluoro-N2-(3-methylaminocarbonylmethyleneoxyphenyl)-N4-[2H-pyrido[3,2-b]-1,4-oxazin-7-yl]-2,4-pyrimidinediamine as a gray solid. ¹H NMR (CDCl₃): δ 2.91 (d, J= 4.8 Hz, 3H), 3.55 (t, J= 4.2 Hz, 2H), 4.24 (t, J= 4.5 Hz, 2H), 4.49 (s, 2H), 4.90 (br, 1H), 6.51 (dd, J= 2.7 and 8.1 Hz, 1H), 6.64 (s, 1H), 6.90 (dd, J= 2.1 and 8.1 Hz, 1H), 7.08 (s, 1H), 7.14 (br, 1H), 7.18 (t, J= 8.1 Hz, 1H), 7.28 (d, J= 2.1 Hz, 1H), 7.51 (t, J= 2.1 Hz, 1H), 7.93 (d, J= 3.0 Hz, 1H), 7.95
 25 (d, J= 2.4 Hz, 1H); LCMS: ret. time: 11.91 min.; purity: 100%; MS (m/e): 426.12 (MH⁺).

7.3.966 5-Fluoro-N2-(3-methylaminocarbonylmethyleneoxyphenyl)-N4-[2H-pyrido[3,2-b]-1,4-oxazin-3(4H)-one-6-yl]-2,4-pyrimidinediamine (R921304)

2H-Pyrido[3,2-b]-1,4-oxazin-3(4H)-one (2.5 g) was dissolved in acetic acid (6 mL) and acetic anhydride (30 mL). Fuming nitric acid (3 mL) was added dropwise to the reaction solution in ice-bath. The reaction solution was stirred in ice-bath overnight.

Solution was poured into crashed ice. The light yellow precipitation was collected by filtration, washed with water and dried to give a mixture of nitrated products (regio-isomers). The mixture was crystallized from dichloromethane to give 6-nitro-2H-pyrido[3,2-b]-1,4-oxazin-3(4H)-one (1 g) as a light yellow solid.

6-Nitro-2H-pyrido[3,2-b]-1,4-oxazin-3(4H)-one (1 g) was reduced under hydrogenolysis conditions using 10% Pd-C in methanol (50 mL) and 1N HCl solution (10 mL) at 50 psi for 2 h. The catalyst was filtered off and washed with methanol and 1N HCl solution. The filtrate was evaporated to give 6-amino-2H-pyrido[3,2-b]-1,4-oxazin-3(4H)-one.

In a manner analogous to the preparation of 5-fluoro-N2-(3-methylaminocarbonylmethyleneoxyphenyl)-N4-[2H-pyrido[3,2-b]-1,4-oxazin-3(4H)-one-7-yl]-2,4-pyrimidinediamine, 6-amino-2H-pyrido[3,2-b]-1,4-oxazin-3(4H)-one was reacted with 2,4-dichloro-5-fluoropyrimidine (500 mg) and 3-methylaminocarbonylmethyleneoxyaniline (500 mg) to give 5-fluoro-N2-(3-methylaminocarbonylmethyleneoxyphenyl)-N4-[2H-pyrido[3,2-b]-1,4-oxazin-3(4H)-one-6-yl]-2,4-pyrimidinediamine as a beige solid. ¹H NMR (DMSO-d₆): δ 2.63 (d, J= 4.5 Hz, 3H), 4.35 (s, 2H), 4.62 (s, 2H), 6.47 (dd, J= 1.8 and 8.1 Hz, 1H), 7.10 (t, J= 8.1 Hz, 1H), 7.25 (d, J= 8.1 Hz, 1H), 7.37 (m, 2H), 7.59 (d, J= 8.4 Hz, 1H), 7.96 (d, J= 5.1 Hz, 1H), 8.13 (d, J= 3.6 Hz, 1H), 9.26 (s, 1H), 9.29 (s, 1H), 11.13 (s, 1H); ¹⁹F NMR (282 MHz, DMSO-d₆): δ - 163.20; LCMS: ret. time: 25.22 min.; purity: 97.55%; MS (m/e): 440.25 (MH⁺).

7.3.967 5-Fluoro-N2-(3-methylaminocarbonylmethyleneoxyphenyl)-N4-[2H-pyrido[3,2-b]-1,4-oxazin-6-yl]-2,4-pyrimidinediamine (R945299)

6-Nitro-2H-pyrido[3,2-b]-1,4-oxazin-3(4H)-one (500 mg) was refluxed with boron hydride methyl sulfide complex (1 mL) in THF (10 mL) for 30 min to give 6-nitro-2H-pyrido[3,2-b]-1,4-oxazine. In a manner analogous to the preparation of 5-fluoro-N2-(3-methylaminocarbonylmethyleneoxyphenyl)-N4-[2H-pyrido[3,2-b]-1,4-oxazin-3(4H)-one-7-yl]-2,4-pyrimidinediamine, 6-nitro-2H-pyrido[3,2-b]-1,4-oxazine was reduced and reacted with 2,4-dichloro-5-fluoropyrimidine (500 mg) and 3-methylaminocarbonylmethyleneoxyaniline (500 mg) to give 5-fluoro-N2-(3-methylaminocarbonylmethyleneoxyphenyl)-N4-[2H-pyrido[3,2-b]-1,4-oxazin-6-yl]-2,4-pyrimidinediamine as a gray solid. ¹H NMR (CD₃OD): δ 2.81 (s, 3H), 3.48 (t, J= 4.5 Hz, 2H), 4.14 (t, J= 4.5 Hz, 2H), 4.44 (s, 2H), 6.60 (ddd, J= 1.5 and 2.7 and 7.5 Hz, 1H), 6.94

(d, J= 8.1 Hz, 1H), 7.14 (d, J= 3.0 Hz, 1H), 7.17 (t, J= 7.8 Hz, 1H), 7.40 (d, J= 8.9 Hz, 1H), 7.42 (t, J= 2.1 Hz, 1H), 7.92 (d, J= 3.3 Hz, 1H); ¹⁹F NMR (282 MHz, CD₃OD): δ - 168.20; LCMS: ret. time: 25.49 min.; purity: 97.56%; MS (m/e): 426.23 (MH⁺).

7.3.968 N4-(1,4-Benzoxazin-3-on-7-yl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine (R908698):

In like manner to N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-(1,4-benzoxazin-3-on-7-yl)pyrimidineamine and 3-aminophenol were reacted to yield N4-(1,4-Benzoxazin-3-on-7-yl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine. ¹H (DMSO-d₆) 8.2 (d, 1H, J=4 Hz), 7.30 (m, 2H), 7.09 (m, 4H), 6.5 (m, 1H), 4.6 (s, 2H) purity 95 %; MS (m/e): 368 (MH⁺)

7.3.969 N2-(1,4-Benzoxazin-3-on-7-yl)- 5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine (R908699):

In like manner to N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-(3-hydroxyphenyl)] pyrimidineamine and 7-amino-1,4-benzoxazine-3-one were reacted to yield N2-(1,4-Benzoxazin-3-on-7-yl)- 5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine. ¹H (DMSO-d₆) 8.20 (d, 1H, J=4 Hz), 7.10 (m, 5H), 6.65 (m, 1H), 4.54 (s, 2H) purity 95 % MS (m/e): 368 (MH⁺)

7.3.970 N4-(1,4-Benzoxazine-3-on-7-yl)-5-fluoro-N2-(N-methyl acetamido-2)-3-phenoxy)-2,4-pyrimidinediamine (R908700):

In like manner to N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-1,4-benzoxazin-3-on-7-yl)phenylpyrimidineamine and 3-(N-methylaminocarbonylmethyleneoxy)aniline were reacted to yield N4-(1,4-Benzoxazine-3-on-7-yl)-5-fluoro-N2-(N-methyl acetamido-2)-3-phenoxy)-2,4-pyrimidinediamine ¹H (DMSO-d₆) 8.2 (d, 1H, J=4 Hz), 8.00 (m, 1H), 7.19 (m, 1H), 7.09 (m, 3H), 6.55 (m, 1H), 4.64 (s, 2H), 4.27 (s, 2H), 3.18 (s, 3H), 2.63 (m, 3H) purity 95 % MS (m/e):439 (MH⁺)

7.3.971 N4-(1,4-Benzoxazine-3-on-6-yl)-5-fluoro-N2-[(N-methyl acetamido-2)-3-phenoxy)]-2,4-pyrimidinediamine (R908701):

In like manner to N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-[6-(1,4-benzoxazin-3-on-yl)]phenylpyrimidineamine and 3-(N-methylaminocarbonylmethyleneoxy)aniline were

reacted to yield N4-(1,4-Benzoxazine-3-on-6-yl)-5-fluoro-N2-[(N-methyl acetamido-2)-3-phenoxy]-2,4-pyrimidinediamine 1H (DMSO-d6) 8.2 (d, 1H, J=4 Hz), 8.00 (m, 1H), 7.13 (m, 3H), 6.95 (m, 1H), 6.55 (m, 1H), 4.64 (s, 2H), 4.27 (s, 2H), 3.18 (s, 3H), 2.63 (m, 3H) purity 96 % MS (m/e): 439 (MH+)

5 **7.3.972 N4-(1,4-Benzoxazine-3-on-6-yl)- 5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine (R908702):**

In like manner to N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-(1,4-benzoxazin-3-on-6-yl)phenylpyrimidineamine and 3-aminophenol were reacted to yield N4-(1,4-Benzoxazine-3-on-6-yl)- 5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine 1H (DMSO-d6) 8.20 (d, 1H, J=4 Hz), 7.22 (m, 2H), 7.03 (m, 4H), 6.55 (m, 1H), 4.64 (s, 2H) purity 98 %MS (m/e): 368 (MH+)

7.3.973 5-Fluoro-N4-(3-hydroxyphenyl)- N2-(N-methyl-1,4-benzoxazine-3-on-6-yl)-2,4-pyrimidinediamine (R908703):

15 In like manner to N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-(N-methyl-1,4-benzoxazin-3-on-6-yl)]phenylpyrimidineamine and 3-(N- methylaminocarbonylmethyleneoxy)aniline were reacted to yield 5-Fluoro-N2-[3-(N-methylaminocarbonylmethyleneoxy)phenyl] -N4-(N-methyl-1,4-benzoxazin-3-on-6-yl)]pyrimidinediamine 1H (DMSO-d6) 8.20 (d, 1H, J=4 Hz), 7.23 (m, 6H), 6.55 (m, 1H), 4.64 (s, 2H), 3.18 (s, 3H) purity 96 %; MS (m/e): 382(MH+)

7.3.974 5-Fluoro-N4-(3-hydroxyphenyl)-N2-(N-methyl-1,4-benzoxazin-7-yl)-2,4-pyrimidinediamine (R908704):

25 In like manner to N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-(N-methyl-1,4-benzoxazin-3-on-7-yl)]phenylpyrimidineamine and 3-(N- methylaminocarbonylmethyleneoxy)aniline were reacted to yield 5-Fluoro-N4-(3-hydroxyphenyl)-N2-(N-methyl-1,4-benzoxazin-7-yl)-2,4-pyrimidinediamine 1H (DMSO-d6) 8.8.13 (d, 1H, J=4 Hz), 7.13 (m, 3H), 6.72 (m, 3H), 6.59 (m, 1H), 4.24 (m, 2H), 4.27 (s, 2H), 3.28 (m, 2H), 2.83 (m, 3H) purity 93 %; MS (m/e): 367 (MH+)

7.3.975 5-Fluoro-N2-[(N-methyl acetamido-2)-3-phenoxy]-N4-(N-methyl-1,4-benzoxazin-7-yl)-2,4-pyrimidinediamine (R908705):

In like manner to N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-(N-methyl-1,4-benzoxazin-3-on-7-yl)]phenylpyrimidineamine and 3-(N-methylaminocarbonylmethyleneoxy)aniline were reacted to yield 5-Fluoro-N2-[(N-methyl acetamido-2)-3-phenoxy]-N4-(N-methyl-1,4-benzoxazin-7-yl)-2,4-pyrimidinediamine 1H (DMSO-d6) 8.20 (d, 1H, J=4 Hz), 7.13 (m, 5H), 6.75 (m, 2H), 4.44 (s, 2H), 4.27 (m, 2H), 3.22 (m, 2H), 2.83 (s, 3H), 2.63 (m, 3H) purity 96 %; MS (m/e): 439 (MH+)

7.3.976 N2-(1,4-Benzoxazin-7-yl)-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine (R908706):

In like manner to N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-(3-hydroxyphenyl)]pyrimidineamine and 7-amino-1,4-benzoxazine were reacted to yield N2-(1,4-Benzoxazin-7-yl)-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine. 1H (DMSO-d6) 7.95 (d, 1H, J=4 Hz), 7.43 (m, 1H), 7.02 (m, 4H), 6.42 (m, 2H), 4.17 (m, 2H), 3.33 (m, 2H) purity 96 %; MS (m/e): 353 (MH+)]

7.3.977 5-Fluoro-N2-(3-hydroxyphenyl)-N4-(N-methyl-1,4-benzoxazin-7-yl)-2,4-pyrimidinediamine (R908707):

In like manner to N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-(N-methyl-1,4-benzoxazin-7-yl)]pyrimidineamine and 3-aminophenol were reacted to yield 5-Fluoro-N2-(3-hydroxyphenyl)-N4-(N-methyl-1,4-benzoxazin-7-yl)-2,4-pyrimidinediamine. 1H (DMSO-d6) 8.20 (d, 1H, J=4 Hz), 7.10 (m, 5H), 6.65 (m, 1H), 4.54 (s, 2H) purity 95 % MS (m/e): 368 (MH+)

7.3.978 5-Fluoro-N4-(3-hydroxyphenyl) N2-(N-Methyl-1,4-benzoxazine-3-on-7-yl)-2,4-pyrimidinediamine (R908708):

In like manner to N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-(3-hydroxyphenyl)]pyrimidineamine and 7-amino-4-N-methyl-1,4-benzoxazine-3-one were reacted to yield 5-Fluoro-N4-(3-hydroxyphenyl) N2-(N-Methyl-1,4-benzoxazine-3-on-7-yl)-2,4-pyrimidinediamine. 1H

(DMSO-d₆) 8.20 (d, 1H, J=4 Hz), 7.23 (m, 1H), 7.15 (m, 5H), 6.62 (m, 1H), 4.64 (s, 2H), 4.27 (s, 2H), 3.18 (s, 3H) purity 95 %; MS (m/e): 380 (MH⁺)

7.3.979 5-Fluoro-N2-(3-hydroxyphenyl)-N4-(N-methyl-1,4-benzoxazin-3-on-6-yl)-2,4-pyrimidinediamine (R908709):

5 In like manner to N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-(3-hydroxyphenyl)pyrimidineamine and 6-amino-1,4-benzoxazine were reacted to yield 5-Fluoro-N2-(3-hydroxyphenyl)-N4-(N-methyl-1,4-benzoxazin-3-on-6-yl)-2,4-pyrimidinediamine. ¹H (DMSO-d₆) 8.20 (d, 1H, J=4 Hz), 7.43 (m, 2H), 7.19 (m, 4H), 6.55 (m, 1H), 4.64 (s, 2H), 3.25 (s, 3H) purity 95 %; MS (m/e): 382 (MH⁺)

7.3.980 5-Fluoro-N2-(3-hydroxyphenyl)-N4-(N-methyl-1,4-benzoxazin-6-yl)-2,4-pyrimidinediamine (R908710):

15 In like manner to N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-(3-hydroxyphenyl)pyrimidineamine and 6-amino-1,4-benzoxazine were reacted to yield 5-Fluoro-N2-(3-hydroxyphenyl)-N4-(N-methyl-1,4-benzoxazin-6-yl)-2,4-pyrimidinediamine. ¹H (MeOD-d₄) 8.20 (d, 1H, J=4 Hz), 7.43 (m, 3H), 6.90 (m, 2H), 6.75 (m, 1H), 4.25 (m, 2H), 3.25 (m, 2H), 2.85 (bs, 1 H) purity 96 %; MS (m/e): 382 (MH⁺)

7.3.981 N4-(1,4-Benzoxazin-7-yl)-5-fluoro-N2-(3-hydroxyphenyl)-pyrimidinediamine (R908711):

20 In like manner to N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, N4-[6-(1,4-benzoxazinyl)]-N2-chloro-5-fluoropyrimidineamine and 3-ethoxycarbonylmethyleneoxyaniline were reacted to yield N4-(1,4-Benzoxazin-7-yl)-5-fluoro-N2-(3-hydroxyphenyl)-pyrimidinediamine ¹H NMR (MeOD-d₄): δ 8.2 (d, 1H, J=4 Hz), 7.15 (m, 4H), 6.84 (m, 2H), 6.62 (m, 1H), 4.65 (s, 2H), 4.15 (m, 4H), 3.28 (m, 2H), 1.19 (t, 3H, J=7 Hz) purity 94 %; MS (m/e): 439 (MH⁺).

7.3.982 (+/-)-5-Fluoro-N2-[(N-methyl acetamido-2)-3-phenoxy]-N4-(2-methyl-1,4-benzoxazin-6-yl)-2,4-pyrimidinediamine (R908712):

30 In like manner to N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, (+/-)-2-chloro-5-fluoro-N4-(2-methyl-1,4-benzoxazin-6-yl)phenylpyrimidineamine and 3-(N-methylaminocarbonylmethyleneoxy)aniline were

reacted to yield (+/-)-5-Fluoro-N2-[(N-methyl acetamido-2)-3-phenoxy]- N4-(2-methyl-1,4-benzoxazin-6-yl)- 2,4-pyrimidinediamine 1H (DMSO-d6) 8.20 (d, 1H, J=4 Hz), 8.13 (m, 1H), 7.1 (m, 5H), 6.96 (m, 1H), 6.63 (m, 1H), 4.62 (m, 1H), 4.40 (s, 3H), 2.63 (m, 3H), 1.25 (m, 3H) purity 93 %; MS (m/e): 453 (MH⁺)

5 **7.3.983 N2-(N-Ethylcarbonylmethyleneoxy-1,4-benzoxazin-6-yl)-5-fluoro-N2-[3-hydroxyphenyl]phenyl]pyrimidinediamine (R908734):**

In like manner to N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-Chloro-5-fluoro-N4-(3-hydroxyphenyl)pyrimidineamine and 6-Amino-N-carbomethoxy-1,4-benzoxazine were reacted to yield N2-(N-Ethylcarbonylmethyleneoxy-1,4-benzoxazin-6-yl)-5-fluoro-N2-[3-hydroxyphenyl]phenyl]pyrimidinediamine 1H NMR (DMSO-d6): δ 8.23 (m, 1H), 7.20 (m, 1H), 7.14 (m, 4H), 6.95(m, 1H), 6.76 (m, 1H), 4.66 (s, 1H), 4.48 (s, 1H), 4.25 (q, 2H J=6.5 Hz), 1.28 (t, 2H, J=6.5 Hz), purity 95 % MS (m/e): 454(MH⁺).

15 **7.3.984 N4-(1,4-Benzoxazin-6-yl)-N2-(3-chloro-4-hydroxy-5-methylphenyl)-5-fluoropyrimidinediamine (R909255):**

In like manner to N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, N4-[6-(1,4-benzoxazinyl)]-N2-chloro-5-fluoropyrimidineamine and 3-chloro-4-hydroxy-5-methylaniline were reacted to yield N4-(1,4-benzoxazin-6-yl)-N2-(3-chloro-4-hydroxy-5-methylphenyl)-5-fluoropyrimidinediamine ¹H NMR (DMSO-d6): δ 7.89 (d, 1H, J=4 Hz), 7.25 (m, 1H), 7.14 (m, 1H), 6.80 (m, 2H), 6.82 (m, 1H), 4.29 (s, 2H), 3.35 (m, 2H), 2.20 (s, 3H) purity 99 %; MS (m/e): 402 (MH⁺).

25 **7.3.985 5-Fluoro-N2-[3-(N-methylaminocarbonylmethyleneoxy)phenyl] -N4-(N-methyl-1,4-benzoxazin-6-yl)pyrimidinediamine (R909259):**

In like manner to N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-[6-(N-methyl-1,4-benzoxazinyl)]phenyl pyrimidineamine and 3-(N-methylaminocarbonylmethyleneoxy)aniline were reacted to yield 5-Fluoro-N2-[3-(N-methylaminocarbonylmethyleneoxy)phenyl]-N4-(N-methyl-1,4-benzoxazin-6-yl)pyrimidinediamine 1H (DMSO-d6) 8.01 (d, 1H, J=4 Hz), 7.33 (m, 2H), 7.22 (m, 1H), 7.02 (m, 2H), 6.65 (m, 1H), 6.42 (m, 1H), 4.37 (s, 2H), 4.22 (m, 2H), 3.18 (m, 2H), 2.78 (s, 3H) 2.63 (m, 3H) purity 98 %; MS (m/e): 439 (MH⁺)

7.3.986 5-Fluoro-N2-[3-(N-methylaminocarbonylmethyleneoxy)phenyl]-N4-[6-(N-methyl-1,4-benzoxazin-3-onyl)]pyrimidinediamine (R909260):

In like manner to N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-
 5 2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-[6-(N-methyl-1,4-benzoxazin-3-onyl)]phenylpyrimidineamine and 3-(N-methylaminocarbonylmethyleneoxy)aniline were reacted to yield 5-Fluoro-N2-[3-(N-methylaminocarbonylmethyleneoxy)phenyl]-N4-[6-(N-methyl-1,4-benzoxazin-3-onyl)]pyrimidinediamine 1H (DMSO-d₆) 8.01 (d, 1H, J=4 Hz), 7.33 (m, 2H), 7.22 (m, 1H), 7.02 (m, 2H), 6.65 (m, 1H), 6.42 (m, 1H), 4.37 (s, 2H), 4.22 (s,
 10 2H), 3.18 (s, 3H), 2.78 (s, 3H) 2.63 (m, 3H) purity 88%; MS (m/e): 453 (MH⁺)

7.3.987 5-Fluoro-N2-[3-(N-methylaminocarbonylmethyleneoxy)phenyl]-N4-(N-methyl-1,4-benzoxazin-3-on-7-yl)-2,4-pyrimidinediamine (R909261):

In like manner to N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-
 15 2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-(N-methyl-1,4-benzoxazin-3-on-7-yl)phenylpyrimidineamine and 3-(N-methylaminocarbonylmethyleneoxy)aniline were reacted to yield 5-Fluoro-N2-[3-(N-methylaminocarbonylmethyleneoxy)phenyl]-N4-(N-methyl-1,4-benzoxazin-3-on-7-yl)pyrimidinediamine 1H (DMSO-d₆) 8.08 (d, 1H, J=4 Hz), 7.43 (m, 2H), 7.19 (m, 1H), 7.09 (m, 3H), 6.55 (m, 1H), 4.64 (s, 2H), 4.27 (s, 2H), 3.18 (s;
 20 3H), 2.63 (m, 3H) MS (m/e): 453 (MH⁺)

7.3.988 (+/-)-5-Fluoro-N4-(3-hydroxyphenyl)-N2-(2-methyl-1,4-benzothiazin-3-on-6-yl)pyrimidinediamine (R909263):

In like manner to N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-
 2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-(3-hydroxyphenyl)pyrimidineamine and 6-
 25 amino-2-methyl-1,4-benzothiazin-3-one were reacted to yield (+/-)-5-Fluoro-N4-(3-hydroxyphenyl)-N2-(2-methyl-1,4-benzothiazin-3-on-6-yl)pyrimidinediamine ¹H NMR (MeOD-d₄): δ8.02 (d, 1H, J=4 Hz), 7.30 (m, 3H), 7.08 (m, 3H), 6.52 (m, 1H), 3.57 (m, 1H), 1.25 (m, 3H) purity 92 %; MS (m/e): 398 (MH⁺).

7.3.989 5-Fluoro-N2-[3-hydroxyphenyl]-N4-(N-methyl-1,4-benzoxazin-3-on-7-yl)-2,4-pyrimidinediamine (R909264):

In like manner to N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-
 2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-(N-methyl-1,4-benzoxazin-3-on-7-yl)]phenylpyrimidineamine and 3-aminophenol were reacted to yield 5-Fluoro-N2-[3-

hydroxyphenyl)-N4-(N-methyl-1,4-benzoxazin-3-on-7-yl)]-2,4-pyrimidinediamine 1H (DMSO-d6) 8.08 (d, 1H, J=4 Hz), 7.53 (m, 2H), 7.09 (m, 4H), 6.42 (m, 1H), 4.64 (s, 2H), 3.27 (s, 3H) purity 95 % MS (m/e): 382 (MH⁺)

5 **7.3.990 N4-(3-Ethylcarboxy-4*H*-imidazo[5,1-*c*]-1,4-benzoxazin-6-yl)-5-fluoro -N2-[3-(N-methylaminocarbonylmethyleneoxy)phenyl]pyrimidinediamine (R909265):**

In like manner to N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, N2-Chloro-N4-(3-ethylcarboxy-4*H*-imidazo[5,1-*c*]-1,4-benzoxazin-6-yl)-5-fluoropyrimidineamine and 3-(N-methylaminocarbonylmethyleneoxy)aniline were
10 reacted to yield N4-(3-Ethylcarboxy-4*H*-imidazo[5,1-*c*]-1,4-benzoxazin-6-yl)-5-fluoro -N2-[3-(N-methylaminocarbonylmethyleneoxy)phenyl]pyrimidinediamine ¹H NMR (DMSO-d6): δ 8.23 (m, 2H), 8.08 (d, J=4 Hz, 1H), 7.92 (m, 1H), 7.43 (m, 1H), 7.38(m, 2H), 7.18 (m, 1H), 6.99 (t, 1H), 6.41 (m, 1H), 5.43 (s, 2H) purity 92 %; MS (m/e): 534 (MH⁺).

15 **7.3.991 N4-(1,4-Benzoxazin-7-yl)-N2-[3-ethoxycarbonylmethyleneoxy)phenyl]-5-fluoro-2,4-pyrimidinediamine (R909266):**

In like manner to N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, N4-(1,4-Benzoxazin-7-yl)-2-chloro-5-fluoro- pyrimidineamine and 3-(ethoxycarbonylmethyleneoxy)aniline were reacted to yield N4-(1,4-Benzoxazin-7-yl)-
20 N2-[3-ethoxycarbonylmethyleneoxy)phenyl]-5-fluoro-2,4-pyrimidinediamine. 1H (DMSO-d6) 8.2 (d, 1H, J=4 Hz), 7.43 (m, 1H), 7.12 (m, 4H), 6.68 (m, 2H), 4.7 (s, 2H) 4.17 (m, 2H), 3.33 (m, 2H), 3.13 (m, 2H) 1.87 (m, 3H) purity 89 %; MS (m/e): 439 (MH⁺)

7.3.992 N2-(3-Ethylcarboxy-4*H*-imidazo[5,1-*c*]-1,4-benzoxazin-6-yl)-5-fluoro-N4-(3-hydroxyphenyl)pyrimidinediamine (R909267):

25 In like manner to N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-Chloro-5-fluoro-N4-(3-hydroxyphenyl)pyrimidineamine and 3 Ethyl 6-Amino-(3-carboxy-4*H*-imidazo[5,1-*c*]-1,4-benzoxazine were reacted to yield N2-(3-Ethylcarboxy-4*H*-imidazo[5,1-*c*]-1,4-benzoxazin-6-yl)-5-fluoro-N4-(3-hydroxyphenyl)pyrimidinediamine 1H NMR (DMSO-d6): δ 8.18 (m, 1H), 8.04 (m, 1H),
30 7.38 (m, 1H), 7.22 (m, 1H), 7.04 (m, 2H), 6.96 (m, 1H), 6.53 (m, 1H), 5.42 (s, 2H), 4.25 (q, 2H J=6.5 Hz), 1.28 (t, 2H, J=6.5 Hz), purity 92 % MS (m/e): 409 (MH⁺).

7.3.993 N2-(1,4-Benzoxazin-3-on-6-yl)- 5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine (R909268)

In like manner to N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine N4-[6-(1,4-benzoxazinyl)]-N2-chloro-5-fluoropyrimidineamine and
 5 6-amino-1,4-benzoxazin-3-one were reacted to yield N2-(1,4-benzoxazin-3-on-6-yl)-5-fluoro-N4-(6-(1,4-benzoxazinyl)]-)-2,4-pyrimidinediamine. ¹H NMR (DMSO-d₆): δ 8.18 (d, 1H J= 4 Hz), 7.17 (m, 2H), 6.88 (m, 2H), 6.80 (m, 1H), 6.58 (m, 1H) 4.52 (s, 2H), 4.11 (m, 2H), 3.33 (m, 2H) purity: 97 %; MS (m/e): 409 (MH⁺).

7.3.994 N2-[3-(N,N-Dimethylaminocarbonylmethyleneoxy) phenyl]-N4-(1,4-benzoxazin-6-yl)-5-fluoro--2,4-pyrimidinediamine (R909290)

In like manner to N4-(3,4-ethylendioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, N4-(1,4-benzoxazin-6-yl)-N2-(3-ethoxyocarbonylmethyleneoxyphenyl)-5-fluoro-pyrimidinediamine and
 15 dimethylamine hydrochloride were reacted to yield N2-[3-(N,N-Dimethylaminocarbonylmethyleneoxy)phenyl] -N4-(1,4-benzoxazin-6-yl) -5-fluoro--2,4-pyrimidinediamine ¹H NMR (CD₃OD): δ 7.8 (d, 1H), 7.4 (m, 1H), 7.05 (m, 2H), 7.0 (s, 1H), 6.8 (dd, 1H), 6.66 (d, 1H), 6.56 (dd, 1H), 4.35 (s, 2H), 4.18 (m, 2H), 3.25 (m, 2H), 2.8 (s, 6H); purity: 95 %; MS (m/e): 439 (MH⁺)

7.3.995 N4-(4N-Carboxamidino-1,4-benzoxazin-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl] -2,4-pyrimidinediamine (R909292)

To a solution in 2 mL THF at 0° Celsius containing 250 mg (0.59 mmol) of N4-(1,4-benzoxazin-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-
 25 pyrimidinediamine, 1.4 eq, 115 uL TEA, and catalytic DMAP was added 0.4 eq, 70 mg of triphosgene. After 30 min 15 mL of aqueous ammonia and stirred for 30 min at RT. The THF was evaporated and the reaction was diluted with water, and the resulting precipitate collection by suction filtration. The crude precipitate was purified by preparative TLC (5% MeOH/EtOAc) to yield N4-(4N-Carboxamidino-1,4-benzoxazin-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. ¹H NMR (CD₃OD): δ
 30 7.83 (m, 1H), 7.42 (m, 1H), 7.12 (m, 2H), 7.08 (s, 1H), 6.84 (m, 1H), 6.66 (m, 1H), 6.48 (m, 1H), 4.30 (s, 2H), 4.15 (m, 2H), 3.22 (m, 2H), 2.82 (s, 3H); purity: 87 %; MS (m/e): 468 (MH⁺).

7.3.996 N4-(3,3-Dimethyl-1,4-benzoxazin-6-yl)-N2-[3-ethoxycarbonylmethyleneoxy)phenyl]-5-fluoro-2,4-pyrimidinediamine (R909308):

In like manner to N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-
5 2,4-pyrimidinediamine, N2-Chloro-N4-(3,3-dimethyl-1,4-benzoxazin-6-yl)-5-fluoro-
pyrimidineamine and 3-(ethoxycarbonylmethyleneoxy)aniline were reacted to yield N4-
(3,3-Dimethyl-1,4-benzoxazin-6-yl)-N2-[3-ethoxycarbonylmethyleneoxy)phenyl]-5-fluoro-
2,4-pyrimidinediamine. ¹H (DMSO-d₆) 8.00 (m, 1H), 7.43 (m, 2H), 7.05 (m, 1H), 6.82 (m,
2H), 6.68 (m, 1H), 6.41 (m, 1H), 4.80 (s, 2H), 4.18 (q, 2H), 3.74 (s, 2 H), 1.03 (t, 3H),
10 1.00 (s, 6H) purity 99 %; MS (m/e): 467 (MH⁺)

7.3.997 N4-(3,3-Dimethyl-1,4-benzoxazin-6-yl)-5-fluoro-N2-[3-(N-methylaminocarbonylmethyleneoxy)phenyl]-2,4-pyrimidinediamine (R909309):

In like manner to N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-
15 methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, N4-(3,3-Dimethyl-1,4-
benzoxazin-6-yl)-N2-[3-ethoxycarbonylmethyleneoxy)phenyl]-5-fluoro-2,4-
pyrimidinediamine and methylamine hydrochloride were reacted to yield N4-(3,3-
Dimethyl-1,4-benzoxazin-6-yl)-5-fluoro-N2-[3-(N-methylaminocarbonyl
methyleneoxy)phenyl]-2,4-pyrimidinediamine. ¹H (DMSO-d₆) 8.04 (d, 1H), 7.93 (m, 1H),
20 7.45 (m, 2H), 7.09 (m, 1H), 6.93 (m, 2H), 6.62 (m, 1H), 6.43 (m, 1H), 4.37 (s, 2H), 3.74
(s, 2 H), 2.62 (d, 3H), 1.07 (s, 6H) purity 99 %; MS (m/e): 453 (MH⁺)

7.3.998 N4-(3,3-Dimethyl-1,4-benzoxazin-6-yl)-5-fluoro-N2-[3-(N-methylaminocarbonylmethyleneoxy)phenyl]-2,4-pyrimidinediamine (R909309):

In like manner to N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-
25 methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, N4-(3,3-Dimethyl-1,4-
benzoxazin-6-yl)-N2-[3-ethoxycarbonylmethyleneoxy)phenyl]-5-fluoro-2,4-
pyrimidinediamine and methylamine hydrochloride were reacted to yield N4-(3,3-
Dimethyl-1,4-benzoxazin-6-yl)-5-fluoro-N2-[3-(N-methylaminocarbonyl
30 methyleneoxy)phenyl]-2,4-pyrimidinediamine. ¹H (DMSO-d₆) 8.04 (d, 1H), 7.93 (m, 1H),
7.45 (m, 2H), 7.09 (m, 1H), 6.93 (m, 2H), 6.62 (m, 1H), 6.43 (m, 1H), 4.37 (s, 2H), 3.74
(s, 2 H), 2.62 (d, 3H), 1.07 (s, 6H) purity 99 %; MS (m/e): 453 (MH⁺)

7.3.999 N4-(2,4-Diiodo-3-hydroxyphenyl)-5-fluoro-N2-(3-iodo-1-methyl-indazoline-5-yl)-2,4-pyrimidinediamine (R935221)

To 5-fluoro-N2-(3-hydroxyphenyl)-N4-(1-methyl-indazoline-5-yl)-2,4-pyrimidinediamine (34.4 mg, 0.098 mmole) in ethanol (2.0 mL) and aq. NH₄OH (2.0 mL),
5 I₂ (0.126 g, 0.99 mmole atom) was added and stirred at room temperature overnight. Reaction mixture was concentrated, dissolved in EtOAc and treated with aq. hypo solution. Organic layer was separated, dried with anhydrous Na₂SO₄ and concentrated. The crude material was purified by silica gel column chromatography to provide N4-(2,4-diiodo-3-hydroxyphenyl)-5-fluoro-N2-[3-iodo-1-methyl-indazoline-5-yl]-2,4-pyrimidinediamine. ¹H
10 NMR (DMSO-d₆): δ 9.86 (s, 1H), 9.51 (s, 1H), 9.12 (s, 1H), 8.28 (s, 1H), 8.07 (d, 1H, J = 3.5 Hz), 7.79 (s, 1H), 7.63 (s, 1H), 7.32 (d, 1H, J = 8.8 Hz), 7.37 (d, 1H, J = 8.8 Hz), 3.92 (s, 3H). LCMS: ret. time: 20.88 min.; purity: 91%; MS (*m/e*): 729 (MH⁺).

7.3.1000 5-Fluoro-N4-(4-isopropoxyphenyl)-N2-[1-(methoxycarbonyl)methyl-indazoline-5-yl]-2,4-pyrimidinediamine (R935222)

In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N-(4-isopropoxyphenyl)-4-pyrimidineamine was reacted with 5-amino-1-(methoxycarbonyl)methylindazoline to provide 5-fluoro-N4-(4-isopropoxyphenyl)-N2-[1-(methoxycarbonyl)methyl-indazoline-5-yl]-2,4-pyrimidinediamine. ¹H NMR (DMSO-d₆): δ 9.17 (s, 1H), 9.13 (s, 1H), 8.10 (s, 1H),
20 8.03 (d, 1H, J = 4.1 Hz), 7.85 (s, 1H), 7.58 (d, 2H, J = 8.8 Hz), 7.46 (s, 2H), 6.87 (s, 2H, J = 8.8 Hz), 5.31 (s, 2H), 4.57 (sep, 1H, J = 5.8 Hz), 3.65 (s, 3H), 1.25 (d, 6H, J = 5.8 Hz). LCMS: ret. time: 21.33 min.; purity: 96%; MS (*m/e*): 451 (MH⁺).

7.3.1001 N4-(3, 4-Ethylenedioxyphenyl)-5-fluoro-N2-[1-(methoxycarbonyl)methyl-indazoline-5-yl]-2,4-pyrimidinediamine (R935223)

In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N-(3, 4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine was reacted with 5-amino-1-(methoxycarbonyl)methyl-indazoline to provide N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-[1-(methoxycarbonyl)methyl-indazoline-5-yl]-2,4-pyrimidinediamine. ¹H NMR (DMSO-d₆): δ 9.16 (s, 1H), 9.14 (s, 1H),
30 8.13 (s, 1H), 8.04 (d, 1H, J = 4.1 Hz), 7.89 (s, 1H), 7.48 (s, 2H), 7.30 (d, 1H, J = 2.9 Hz),

7.20 (dd, 1H, J = 2.9 and 8.8 Hz), 6.79 (d, 1H, J = 8.8 Hz), 5.32 (s, 2H), 4.22 (s, 4H), 3.65 (s, 3H). LCMS: ret. time: 21.33 min.; purity: 96%; MS (*m/e*): 451 (MH⁺).

7.3.1002 5-Fluoro-N2-(4-isopropoxyphenyl)-N4-[1-(*N*-methylaminocarbonyl)methyl-indazoline-6-yl]-2,4-pyrimidinediamine (R935224)

In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(*N*-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, 5-fluoro-N2-(4-isopropoxyphenyl)-N2-[1-(methoxycarbonyl)methyl-indazoline-6-yl]-2,4-pyrimidinediamine and Me₂NH.HCl were reacted to provide 5-fluoro-N2-(4-isopropoxyphenyl)-N4-[1-(*N*-methylaminocarbonyl)methyl-indazoline-6-yl]-2,4-pyrimidinediamine. ¹H NMR (DMSO-d₆): δ 9.46 (s, 1H), 8.98 (s, 1H), 8.07 (d, 1H, J = 4.1 Hz), 8.02 (d, 1H, J = 4.7 Hz), 7.98 (s, 2H), 7.66 (d, 1H, J = 8.8 Hz), 7.50 (d, 2H, J = 8.8 Hz), 7.46 (app s, 1H), 6.74 (d, 2H, J = 8.8 Hz), 4.96 (s, 2H), 4.46 (sept, 1H, J = 5.8 Hz), 2.58 (d, 3H, J = 4.7 Hz), 1.21 (d, 6H, J = 5.8 Hz). LCMS: ret. time: 18.22 min.; purity: 93%; MS (*m/e*): 450 (MH⁺).

7.3.1003 N2-(3, 4-Ethylenedioxyphenyl)-5-fluoro-N4-[1-(*N*-methylaminocarbonyl)methyl-indazoline-6-yl]-2,4-pyrimidinediamine (R935225)

In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(*N*-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, N2-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-[1-(methoxycarbonyl)methyl-indazoline-6-yl]-2,4-pyrimidinediamine and Me₂NH.HCl were reacted to provide N2-(3, 4-ethylenedioxyphenyl)-5-fluoro-N4-[1-(*N*-methylaminocarbonyl)methyl-indazoline-6-yl]-2,4-pyrimidinediamine. ¹H NMR (DMSO-d₆): δ 9.47 (s, 1H), 8.99 (s, 1H), 8.08 (d, 1H, J = 3.5 Hz), 8.06 (s, 1H), 8.01 (d, 1H, J = 4.7 Hz), 7.98 (d, 1H, J = 1.1 Hz), 7.66 (d, 1H, J = 8.8 Hz), 7.45 (dd, 1H, J = 1.1 and 8.8 Hz), 7.31 (d, 1H, J = 2.3 Hz), 7.01 (dd, 1H, J = 2.9 and 8.8 Hz), 6.66 (d, 1H, J = 8.8 Hz), 4.95 (s, 2H), 4.14 (s, 4H), 2.57 (d, 3H, J = 4.1 Hz). LCMS: ret. time: 15.55 min.; purity: 94%; MS (*m/e*): 450 (MH⁺).

7.3.1004 5-Fluoro-N4-(3-hydroxyphenyl)-N2-[1-(methoxycarbonyl)methyl-indazoline-5-yl]-2,4-pyrimidinediamine (R935237)

In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N-(3-hydroxyphenyl)-4-

pyrimidineamine was reacted with 5-amino-1-(methoxycarbonyl)methyl-indazoline to produce 5-fluoro-N4-(3-hydroxyphenyl)-N2-[1-(methoxycarbonyl)methyl-indazoline-5-yl]-2,4-pyrimidinediamine. ¹H NMR (DMSO-d₆): δ 9.40 (s, 1H), 9.19 (s, 1H), 9.17 (s, 1H), 8.23 (s, 1H), 8.07 (d, 1H, J = 3.5 Hz), 7.90 (s, 1H), 7.47 (s, 2H), 7.25 (d, 1H, J = 7.6 Hz), 7.11 (d, 1H, J = 7.6 Hz), 7.08 (d, 1H, J = 8.2 Hz), 6.53 (d, 1H, J = 8.2 Hz), 5.31 (s, 2H), 3.64 (s, 3H). LCMS: ret. time: 15.82 min.; purity: 96%; MS (*m/e*): 409 (MH⁺).

7.3.1005 N2, N4-Bis[1-(2-hydroxyethyl)indazoline-6-yl]-5-fluoro-2,4-pyrimidinediamine (R935238)

In like manner to the preparation of N2-(3, 4-ethylenedioxyphenyl)-5-fluoro-N4-[4(2-hydroxy-1,1-dimethylethyl)phenyl]-2,4-pyrimidinediamine, N2, N4-bis[1-(methoxycarbonyl)methyl-indazoline-6-yl]-5-fluoro-2,4-pyrimidinediamine was reacted with DIBAL-H to produce N2, N4-bis[1-(2-hydroxyethyl)indazoline-6-yl]-5-fluoro-2,4-pyrimidinediamine. ¹H NMR (DMSO-d₆): δ 9.56 (s, 1H), 9.43 (s, 1H), 8.19 (d, 1H, J = 3.5 Hz), 8.06 (s, 1H), 8.03 (s, 1H), 7.98 (s, 1H), 7.86 (s, 1H), 7.66 (d, 1H, J = 8.8 Hz), 7.52 (d, 1H, J = 8.8 Hz), 7.42 (dd, 1H, J = 1.7 and 8.8 Hz), 7.23 (dd, 1H, J = 1.7 and 8.8 Hz), 4.75 (t, 1H, J = 5.3 Hz), 4.68 (t, 1H, J = 5.3 Hz), 4.09-4.02 (m, 2H), 3.81-3.74 (m, 2H), 3.63-3.60 (m, 2H), 3.56-3.52 (m, 2H). LCMS: ret. time: 13.73 min.; purity: 90%; MS (*m/e*): 449 (MH⁺).

7.3.1006 5-Fluoro-N4-(4-isopropoxyphenyl)-N2-[1-(N-methylaminocarbonyl)methyl-indazoline-5-yl]-2,4-pyrimidinediamine (R935239)

In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, 5-fluoro-N4-(4-isopropoxyphenyl)-N2-[1-(methoxycarbonyl)methyl-indazoline-5-yl]-2,4-pyrimidinediamine and Me₂NH.HCl were reacted to provide 5-fluoro-N4-(4-isopropoxyphenyl)-N2-[1-(N-methylaminocarbonyl)methyl-indazoline-5-yl]-2,4-pyrimidinediamine. ¹H NMR (DMSO-d₆): δ 9.27 (s, 1H), 9.21 (s, 1H), 8.07 (s, 1H), 8.04 (d, 1H, J = 4.1 Hz), 7.90 (qt, 1H, J = 4.7 Hz), 7.83 (s, 1H), 7.58 (d, 2H, J = 8.8 Hz), 7.44 (s, 2H), 6.87 (d, 2H, J = 8.8 Hz), 4.98 (s, 2H), 4.57 (q, 1H, J = 5.8 Hz), 2.59 (d, 3H, J = 4.1 Hz), 1.21 (d, 6H, J = 5.8 Hz). LCMS: ret. time: 17.74 min.; purity: 94%; MS (*m/e*): 450 (MH⁺).

7.3.1007 N4-(3, 4-Ethylenedioxyphenyl)-5-fluoro-N2-[1-(N-methylaminocarbonyl)methyl-indazoline-5-yl]-2,4-pyrimidinediamine (R935240)

In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-[1-(methoxycarbonyl)methyl-indazoline-5-yl]-2,4-pyrimidinediamine and Me₂NH.HCl were reacted to provide N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-[1-(N-methylaminocarbonyl)methyl-indazoline-5-yl]-2,4-pyrimidinediamine. ¹H NMR (DMSO-d₆): δ 9.36 (br s, 2H), 8.06 (d, 1H, J = 3.5 Hz), 8.05 (s, 1H), 7.99 (qt, 1H, J = 4.7Hz), 7.87 (s, 1H), 7.46 (s, 2H), 7.30-7.28 (m, 1H), 7.20-7.17 (m, 1H), 6.79 (d, 1H, J = 8.8 Hz), 4.99 (s, 2H), 4.22 (s, 4H), 2.59 (d, 3H, J = 4.7 Hz). LCMS: ret. time: 15.06 min.; purity: 91%; MS (m/e): 450 (MH⁺).

7.3.1008 5-Fluoro-N2-(4-isopropoxyphenyl)-N4-[1-(methoxycarbonyl)methyl-indazoline-5-yl]-2,4-pyrimidinediamine (R935242)

In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N-[1-(methoxycarbonyl)methyl-indazoline-5-yl]-4-pyrimidineamine was reacted with 4-isopropoxyaniline to provide 5-fluoro-N2-(4-isopropoxyphenyl)-N4-[1-(methoxycarbonyl)methyl-indazoline-5-yl]-2,4-pyrimidinediamine. ¹H NMR (DMSO-d₆): δ 10.58 (s, 1H), 10.09 (s, 1H), 8.23 (d, 1H, J = 5.3 Hz), 8.04 (s, 1H), 8.02 (s, 1H, J = 5.8 Hz), 7.68-7.63 (m 1H), 7.58-7.55 (s, 1H), 7.30 (d, 2H, J = 8.8 Hz), 6.82 (d, 2H, J = 8.8 Hz), 5.41 (s, 2H), 4.53 (sept, 1H, J = 5.8 Hz), 3.66 (s, 3H), 1.21 (d, 6H, J = 5.8 Hz). LCMS: ret. time: 19.30 min.; purity: 93%; MS (m/e): 451 (MH⁺).

7.3.1009 N4-(3, 4-Ethylenedioxyphenyl)-5-fluoro-N2-[1-(2-hydroxyethyl)indazoline-6-yl]-2,4-pyrimidinediamine (R935248)

In like manner to the preparation of N2-(3, 4-ethylenedioxyphenyl)-5-fluoro-N4-[4(2-hydroxy-1,1-dimethylethyl)phenyl]-2,4-pyrimidinediamine, N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-[1-(methoxycarbonyl)methyl-indazoline-6-yl]-2,4-pyrimidinediamine was reacted with DIBAL-H to produce N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-[1-(2-hydroxyethyl)indazoline-6-yl]-2,4-pyrimidinediamine. LCMS: ret. time: 19.42 min.; purity: 94%; MS (m/e): 423 (MH⁺).

7.3.1010 N2-(3, 4-Ethylenedioxyphenyl)-5-fluoro-N4-[1-(methoxycarbonyl)methyl-indazoline-5-yl]-2,4-pyrimidinediamine (R935249)

In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N-[1-(methoxycarbonyl)methyl-indazoline-5-yl]-4-pyridinamine was reacted with 3, 4-ethylenedioxyaniline to provide N2-(3, 4-ethylenedioxyphenyl)-5-fluoro-N4-[1-(methoxycarbonyl)methyl-indazoline-5-yl]-2,4-pyrimidinediamine. ¹H NMR (DMSO-d₆): δ 9.32 (s, 1H), 8.94 (s, 1H), 8.14 (d, 1H, J = 4.7 Hz), 8.03 (d, 1H, J = 4.7 Hz), 8.01 (s, 1H), 7.65-7.57 (m, 2H), 7.23 (d, 1H, J = 1.7 Hz), 7.02 (dd, 1H, J = 1.9 and 8.8 Hz), 6.63 (d, 1H, J = 8.8 Hz), 5.38 (s, 2H), 4.14 (s, 4H), 3.66 (s, 3H). LCMS: ret. time: 18.94 min.; purity: 91%; MS (*m/e*): 451 (MH⁺).

7.3.1011 5-Fluoro-N2-(3-hydroxyphenyl)-N4-[1-(methoxycarbonyl)methyl-indazoline-5-yl]-2,4-pyrimidinediamine (R935250)

In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N-[1-(methoxycarbonyl)methyl-indazoline-5-yl]-4-pyrimidineamine was reacted with 3-aminophenol to provide 5-fluoro-N2-(3-hydroxyphenyl)-N4-[1-(methoxycarbonyl)methyl-indazoline-5-yl]-2,4-pyrimidinediamine. ¹H NMR (DMSO-d₆): δ 9.34 (s, 1H), 9.16 (s, 1H), 8.25 (d, 1H, J = 4.7 Hz), 8.05 (d, 1H, J = 4.7 Hz), 8.02 (s, 1H), 7.65-7.57 (m, 2H), 7.10 (d, 2H, J = 5.8 Hz), 6.93 (d, 1H, J = 8.8 Hz), 6.90 (d, 1H, J = 8.8 Hz), 6.28 (app d, 1H, J = 8.8 Hz), 5.37 (s, 2H), 3.66 (s, 3H). LCMS: ret. time: 17.87 min.; purity: 97%; MS (*m/e*): 409 (MH⁺).

7.3.1012 5-Fluoro-N4-(4-isopropoxyphenyl)-N2-(1H-pyrrol-1-yl)-2,4-pyrimidinediamine (R935251)

In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N-(4-isopropoxyphenyl)-4-pyrimidineamine was reacted with 1-aminopyrrole to provide 5-fluoro-N4-(4-isopropoxyphenyl)-N2-(1H-pyrrol-1-yl)-2,4-pyrimidinediamine. ¹H NMR (DMSO-d₆): δ 9.93 (s, 1H), 9.21 (s, 1H), 7.97 (d, 1H, J = 4.1 Hz), 7.47 (d, 2H, J = 8.8 Hz), 6.70 (dd, 2H, J = 2.3 and 4.7 Hz), 6.67 (d, 2H, J = 8.8 Hz), 6.02 (dd, 2H, J = 2.3 and 4.7 Hz), 4.48 (sept, 1H, J = 5.8 Hz), 1.21 (d, 6H, J = 5.8 Hz). LCMS: ret. time: 23.44 min.; purity: 90%; MS (*m/e*): 328 (MH⁺).

7.3.1013 N4-(3, 4-Ethylenedioxyphenyl)-5-fluoro-N2-(1H-pyrrol-1-yl)-2,4-pyrimidinediamine (R935252)

In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N-(3, 4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine was reacted with 1-aminopyrrole to provide N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(1H-pyrrol-1-yl)-2,4-pyrimidinediamine. ¹H NMR (DMSO-d₆): δ 9.95 (s, 1H), 9.16 (s, 1H), 7.95 (d, 1H, J = 3.5 Hz), 7.16-7.12 (m, 2H), 6.69 (dd, 2H, J = 2.3 and 4.7 Hz), 6.61 (d, 1H, J = 8.8 Hz), 5.99 (dd, 2H, J = 2.3 and 4.7 Hz), 4.12-4.15 (m, 4H). LCMS: ret. time: 19.86 min.; purity: 92%; MS (m/e): 328 (MH⁺).

7.3.1014 5-Fluoro-N4-(3-hydroxyphenyl)-N2-(1H-pyrrol-1-yl)-2,4-pyrimidinediamine (R935253)

In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N-(3-hydroxyphenyl)-4-pyrimidineamine was reacted with 1-aminopyrrole to provide 5-fluoro-N4-(3-hydroxyphenyl)-N2-(1H-pyrrol-1-yl)-2,4-pyrimidinediamine. ¹H NMR (DMSO-d₆): δ 9.95 (s, 1H), 9.22 (s, 1H), 9.19 (s, 1H), 7.99 (d, 1H, J = 3.5 Hz), 7.22 (d, 1H, J = 8.2 Hz), 6.94 (br s, 1H), 6.89 (t, 1H, J = 8.2 Hz), 6.70 (dd, 2H, J = 2.3 and 4.7 Hz), 6.38 (d, 1H, J = 8.2 Hz), 5.99 (t, 2H, J = 2.3 and 4.7 Hz). LCMS: ret. time: 18.23 min.; purity: 94%; MS (m/e): 286 (MH⁺).

7.3.1015 5-Fluoro-N2-[1-(2-hydroxyethyl)indazoline-5-yl]-N4-(4-isopropoxyphenyl)-2,4-pyrimidinediamine (R935255)

In like manner to the preparation of N2-(3, 4-ethylenedioxyphenyl)-5-fluoro-N4-[4(2-hydroxy-1,1-dimethylethyl)phenyl]-2,4-pyrimidinediamine, 5-fluoro-N4-(4-isopropoxyphenyl)-N2-[1-(methoxycarbonyl)methyl-indazoline-5-yl]-2,4-pyrimidinediamine was reacted with DIBAL-H to produce 5-fluoro-N2-[1-(2-hydroxyethyl)indazoline-5-yl]-N4-(4-isopropoxyphenyl)-2,4-pyrimidinediamine. ¹H NMR (DMSO-d₆): δ 9.16 (s, 1H), 9.10 (s, 1H), 8.09 (s, 1H), 8.02 (s, 1H, J = 4.0 Hz), 7.79 (s, 1H), 7.59 (d, 2H, J = 8.8 Hz), 7.48 (d, 1H, J = 8.8 Hz), 7.42 (dd, 1H, J = 1.7 and 8.8 Hz), 6.87 (d, 2H, J = 8.8 Hz), 4.83 (t, 1H, J = 5.8 Hz), 4.57 (sept, 1H, J = 5.8 Hz), 4.35 (t, 2H, J = 5.8 Hz), 3.75 (app qt, 2H, J = 5.8 Hz), 1.26 (d, 6H, J = 5.8 Hz). LCMS: ret. time: 20.90 min.; purity: 94%; MS (m/e): 423 (MH⁺).

7.3.1016 5-Fluoro-N2-[1-(2-hydroxyethyl)indazoline-5-yl]-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine (R935256)

In like manner to the preparation of N2-(3, 4-ethylenedioxyphenyl)-5-fluoro-N4-[4(2-hydroxy-1,1-dimethylethyl)phenyl]-2,4-pyrimidinediamine, 5-fluoro-N4-(3-hydroxyphenyl)-N2-[1-(methoxycarbonyl)methyl-indazoline-5-yl]-2,4-pyrimidinediamine was reacted with DIBAL-H to produce 5-fluoro-N2-[1-(2-hydroxyethyl)indazoline-5-yl]-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine. ¹H NMR (DMSO-d₆): δ 9.39 (s, 1H), 9.18 (s, 1H), 9.14 (s, 1H), 8.19 (s, 1H), 8.07 (d, 1H, J = 4.1 Hz), 7.84 (s, 1H), 7.50-7.42 (m, 2H), 7.26 (d, 1H, J = 8.2 Hz), 7.12-7.06 (m, 2H), 6.52 (d, 1H, J = 8.2 Hz), 4.83 (t, 1H, J = 5.8 Hz), 4.35 (t, 2H, J = 5.8 Hz), 3.75 (app qt, 2H, J = 5.8 Hz). LCMS: ret. time: 15.97 min.; purity: 95%; MS (*m/e*): 381 (MH⁺).

7.3.1017 N2-(3, 4-Ethylenedioxyphenyl)-5-fluoro-N4-[1-(2-hydroxyethyl)indazoline-5-yl]-2,4-pyrimidinediamine (R935258)

In like manner to the preparation of N2-(3, 4-ethylenedioxyphenyl)-5-fluoro-N4-[4(2-hydroxy-1,1-dimethylethyl)phenyl]-2,4-pyrimidinediamine, N2-(3, 4-ethylenedioxyphenyl)-5-fluoro-N4-[1-(methoxycarbonyl)methyl-indazoline-5-yl]-2,4-pyrimidinediamine was reacted with DIBAL-H to produce N2-(3, 4-ethylenedioxyphenyl)-5-fluoro-N4-[1-(2-hydroxyethyl)indazoline-5-yl]-2,4-pyrimidinediamine. ¹H NMR (DMSO-d₆): δ 9.20 (s, 1H), 8.93 (s, 1H), 8.12 (s, 1H), 8.02 (d, 1H, J = 3.5 Hz), 7.94 (s, 1H), 7.59 (s, 2H), 7.23 (d, 1H, J = 0.9 Hz), 7.02 (dd, 1H, J = 1.0 and 8.8 Hz), 6.64 (d, 1H, J = 8.8 Hz), 4.86 (t, 1H, J = 5.3 Hz), 4.40 (t, 2H, J = 5.8 Hz), 4.15 (s, 4H), 3.78 (app qt, 2H, J = 5.3 and 5.8 Hz). LCMS: ret. time: 18.07 min.; purity: 93%; MS (*m/e*): 423 (MH⁺).

7.3.1018 5-Fluoro-N4-[1-(2-hydroxyethyl)indazoline-5-yl]-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine (R935259)

In like manner to the preparation of N2-(3, 4-ethylenedioxyphenyl)-5-fluoro-N4-[4(2-hydroxy-1,1-dimethylethyl)phenyl]-2,4-pyrimidinediamine, 5-fluoro-N2-(3-hydroxyphenyl)-N4-[1-(methoxycarbonyl)methyl-indazoline-5-yl]-2,4-pyrimidinediamine was reacted with DIBAL-H to produce 5-fluoro-N4-[1-(2-hydroxyethyl)indazoline-5-yl]-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine. ¹H NMR (DMSO-d₆): δ 9.31 (s, 1H), 9.16 (s, 1H), 9.01 (s, 1H), 8.23 (s, 1H), 8.05 (d, 1H, J = 3.5 Hz), 7.96 (s, 1H), 7.60 (s, 2H), 7.10 (app s, 2H), 6.92 (t, 1H, J = 8.8 Hz), 6.31 (d, 1H, J = 8.8 Hz), 4.86 (t, 1H, J = 5.3 Hz), 4.40

(t, 2H, J = 5.8 Hz), 3.79 (app qt, 2H, J = 5.3 and 5.8 Hz). LCMS: ret. time: 16.09 min.; purity: 89%; MS (*m/e*): 381 (MH⁺).

7.3.1019 N2-(3, 4-Ethylenedioxyphenyl)-5-fluoro-N4-(indazoline-6-yl)-2,4-pyrimidinediamine (R935261)

5 In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N-(indazoline-6-yl)-4-pyrimidineamine was reacted 3, 4-ethylenedioxyaniline to produce N2-(3, 4-ethylenedioxyphenyl)-5-fluoro-N4-(indazoline-6-yl)-2,4-pyrimidinediamine. ¹H NMR (DMSO-d₆): δ 12.85 (s, 1H), 9.40 (s, 1H), 9.01 (s, 1H), 8.07 (d, 1H, J = 3.5 Hz), 7.97 (s, 10 1H), 7.86 (s, 1H), 7.65 (d, 1H, J = 8.8 Hz), 7.47 (dd, 1H, J = 2.3 and 8.8 Hz), 7.27 (d, 1H, J = 2.3 Hz), 7.07 (dd, 1H, J = 2.3 and 8.8 Hz), 6.64 (dd, 1H, J = 1.7 and 8.8 Hz), 4.14 (s, 4H). LCMS: ret. time: 15.90 min.; purity: 100%; MS (*m/e*): 379 (MH⁺).

7.3.1020 5-Fluoro-N2-(3-hydroxyphenyl)-N4-(indazoline-6-yl)-2,4-pyrimidinediamine (R935262)

15 In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N-(indazoline-6-yl)-4-pyrimidineamine was reacted with 3-aminophenol to produce 5-fluoro-N2-(3-hydroxyphenyl)-N4-(indazoline-6-yl)-2,4-pyrimidinediamine. ¹H NMR (DMSO-d₆): δ 10.80 (s, 1H), 10.49 (s, 1H), 8.35 (d, 1H, J = 5.3 Hz), 8.06 (s, 1H), 7.78 (d, 1H), 7.75 (d, 20 1H, J = 8.8 Hz), 7.42 (dd, 1H, J = 1.7 and 8.8 Hz), 6.99-6.97 (m, 2H), 6.80 (s, 1H), 6.52-6.48 (m, 1H). LCMS: ret. time: 13.78 min.; purity: 100%; MS (*m/e*): 379 (MH⁺).

7.3.1021 N2-(3-Chloro-4-hydroxy-3-methylphenyl)-5-fluoro-N4-[4H-imidazo[2,1-c][1,4]-benzoxazin-8-yl]-2,4-pyrimidinediamine (R935263)

25 In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N-[4H-imidazo[2,1-c][1,4]-benzoxazin-8-yl]-4-pyrimidineamine was reacted with 4-amino-2-chloro-6-methylphenol to produce N2-(3-chloro-4-hydroxy-3-methylphenyl)-5-fluoro-N4-[4H-imidazo[2,1-c][1,4]-benzoxazin-8-yl]-2,4-pyrimidinediamine. ¹H NMR (DMSO-d₆): δ 9.40 (s, 1H), 9.04 (s, 30 1H), 8.51 (s, 1H), 8.07 (d, 1H, J = 3.5 Hz), 7.98 (d, 1H, J = 2.3 Hz), 7.67 (s, 1H), 7.53 (s, 1H), 7.41-7.36 (m, 1H), 7.20 (s, 1H), 7.10 (d, 1H, J = 8.8 Hz), 7.07 (s, 1H), 5.24 (s, 2H), 1.98 (s, 3H). LCMS: ret. time: 13.36 min.; purity: 90%; MS (*m/e*): 439 (MH⁺).

7.3.1022 N2-(3-Chloro-4-hydroxy-3-methylphenyl)-5-fluoro-N4-(indazoline-6-yl)-2,4-pyrimidinediamine (R935264)

In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N-(indazoline-6-yl)-4-pyrimidineamine was reacted with 4-amino-2-chloro-6-methylphenol to produce N2-(3-chloro-4-hydroxy-3-methylphenyl)-5-fluoro-N4-(indazoline-6-yl)-2,4-pyrimidinediamine. ¹H NMR (DMSO-d₆): δ 9.62 (s, 1H), 9.19 (s, 1H), 8.61 (s, 1H), 8.12 (s, 1H), 8.02 (s, 1H), 7.77 (s, 1H), 7.67 (d, 1H, J = 8.8 Hz), 7.50-7.45 (m, 2H), 7.26 (s, 1H), 1.98 (s, 3H). LCMS: ret. time: 13.78 min.; purity: 100%; MS (*m/e*): 385 (MH⁺).

7.3.1023 5-Fluoro-N4-(indazoline-5-yl)-N2-(4-isopropoxyphenyl)-2,4-pyrimidinediamine (R935266)

In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N-(indazoline-5-yl)-4-pyrimidineamine was reacted with 4-isopropoxyaniline to produce 5-fluoro-N4-(indazoline-5-yl)-N2-(4-isopropoxyphenyl)-2,4-pyrimidinediamine. ¹H NMR (DMSO-d₆): δ 10.30 (s, 1H), 9.80 (s, 1H), 8.16 (d, 1H, J = 5.3 Hz), 8.06 (s, 1H), 7.98 (s, 1H), 7.51 (s, 2H), 7.32 (d, 2H, J = 8.8 Hz), 6.79 (d, 2H, J = 8.8 Hz), 4.51 (sept, 1H, J = 5.8 Hz), 1.22 (d, 6H, J = 5.8 Hz). LCMS: ret. time: 17.65 min.; purity: 98%; MS (*m/e*): 379 (MH⁺).

7.3.1024 N2-(3, 4-Ethylenedioxyphenyl)-5-fluoro-N4-(indazoline-5-yl)-2,4-pyrimidinediamine (R935267)

In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N-(indazoline-5-yl)-4-pyrimidineamine was reacted with 3, 4-ethylenedioxyphenylaniline to produce N2-(3, 4-ethylenedioxyphenyl)-5-fluoro-N4-(indazoline-5-yl)-2,4-pyrimidinediamine. ¹H NMR (DMSO-d₆): δ 10.20 (s, 1H), 9.61 (s, 1H), 8.13 (d, 1H, J = 5.3 Hz), 8.08 (s, 1H), 7.98 (s, 1H), 7.54-7.48 (m, 2H), 7.06 (d, 1H, J = 2.3 Hz), 6.90 (dd, 1H, J = 2.3 and 8.8 Hz), 6.72 (d, 1H, J = 8.8 Hz), 4.17 (s, 4H). LCMS: ret. time: 15.16 min.; purity: 100%; MS (*m/e*): 379 (MH⁺).

7.3.1025 5-Fluoro-N2-(3-hydroxyphenyl)-N4-(indazoline-5-yl)-2,4-pyrimidinediamine (R935268)

In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N-(indazoline-5-yl)-4-

pyrimidineamine was reacted with 3-aminophenol to produce 5-fluoro-N2-(3-hydroxyphenyl)-N4-(indazoline-5-yl)-2,4-pyrimidinediamine. ¹H NMR (DMSO-d₆): δ 10.64 (s, 1H), 10.33 (s, 1H), 8.29 (d, 1H, J = 5.3 Hz), 8.12 (s, 1H), 8.03 (s, 1H), 7.55 (dd, 2H, J = 1.7 and 8.8 Hz), 7.00 (d, 1H, J = 8.8 Hz), 6.90 (d, 1H, J = 8.8 Hz), 6.85 (d, 1H, J = 1.7 Hz), 6.53 (d, 1H, J = 8.8 Hz). LCMS: ret. time: 12.80 min.; purity: 98%; MS (*m/e*): 337 (MH⁺).

7.3.1026 5-Fluoro-N4-(indazoline-5-yl)-N2-[3-(methoxycarbonylmethyleneoxy)phenyl]-2,4-pyrimidinediamine (R935269)

In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N-(indazoline-5-yl)-4-pyrimidineamine was reacted with 3-(methoxycarbonylmethyleneoxy)aniline to produce 5-fluoro-N4-(indazoline-5-yl)-N2-[3-(methoxycarbonylmethyleneoxy)phenyl]-2,4-pyrimidinediamine. ¹H NMR (DMSO-d₆): δ 10.64 (s, 1H), 9.82 (s, 1H), 8.20 (d, 1H, J = 4.6 Hz), 8.10 (s, 1H), 8.08 (s, 1H), 7.99 (s, 1H), 7.57 (m, 2H), 7.13-7.6 (m, 3H), 6.56 (d, 1H, J = 8.8 Hz), 4.60 (s, 2H), 3.65 (s, 3H). LCMS: ret. time: 15.36 min.; purity: 94%; MS (*m/e*): 409 (MH⁺).

7.3.1027 5-Fluoro-N4-(indazoline-5-yl)-N2-(indazoline-6-yl)-2,4-pyrimidinediamine (R935270)

In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N-(indazoline-5-yl)-4-pyrimidineamine was reacted with 6-aminoindazoline to produce 5-fluoro-N4-(indazoline-5-yl)-N2-(indazoline-6-yl)-2,4-pyrimidinediamine. ¹H NMR (DMSO-d₆): δ 10.35 (s, 1H), 9.19 (s, 1H), 8.25 (d, 1H, J = 4.1 Hz), 8.12 (s, 1H), 8.01 (s, 1H), 7.81 (s, 1H), 7.73 (s, 1H), 7.64 (d, 1H, J = 8.8 Hz), 7.60 (dd, 2H, J = 1.7 and 8.9 Hz), 7.51 (d, 1H, J = 8.9 Hz), 7.21 (dd, 1H, J = 1.7 and 8.8 Hz). LCMS: ret. time: 13.45 min.; purity: 95%; MS (*m/e*): 361 (MH⁺).

7.3.1028 5-Fluoro-N4-[4H-imidazo[2,1-*c*][1,4]-benzoxazin-8-yl]-N2-[3-(*N*-methylaminocarbonylmethyleneoxy)phenyl]-2,4-pyrimidinediamine (R935271)

In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N-[4H-imidazo[2,1-*c*][1,4]-benzoxazin-8-yl]-4-pyrimidineamine was reacted with 3-(*N*-

methylaminocarbonylmethyleneoxy)aniline to produce 5-fluoro-N4-[4H-imidazo[2,1-c][1,4]-benzoxazin-8-yl]-N2-[3-(N-methylaminocarbonylmethyleneoxy)phenyl]-2,4-pyrimidinediamine. ¹H NMR (DMSO-d₆): δ 9.44 (s, 1H), 9.25 (s, 1H), 8.11 (d, 1H, J = 3.5 Hz), 8.03 (d, 1H, J = 2.3 Hz), 7.90 (qt, 1H, J = 4.6 Hz), 7.69 (d, 1H, J = 1.2 Hz), 7.47–7.42 (m, 1H), 7.33 (m, 1H), 7.26 (dd, 1H, J = 1.2 and 8.2 Hz), 7.12 (s, 1H), 7.09 (d, 1H, J = 1.7 Hz), 6.97 (t, 1H, J = 8.2 Hz), 6.40 (dd, 1H, J = 2.3 and 8.2 Hz), 5.25 (s, 2H), 4.26 (s, 2H), 2.61 (d, 3H, J = 4.6 Hz). LCMS: ret. time: 15.45 min.; purity: 97%; MS (m/e): 462 (MH⁺).

7.3.1029 5-Fluoro-N2-(4-isopropoxyphenyl)-N4-(1H-pyrrol-1-yl)- 2,4-pyrimidinediamine (R935276)

In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N-(1H-pyrrol-1-yl)-4-pyrimidineamine was reacted with 4-isopropoxyaniline to produce 5-fluoro-N2-(4-isopropoxyphenyl)-N4-(1H-pyrrol-1-yl)- 2,4-pyrimidinediamine. ¹H NMR (DMSO-d₆): δ 10.69 (s, 1H), 9.03 (s, 1H), 8.06 (d, 1H, J = 3.5 Hz), 7.30 (d, 2H, J = 9.3 Hz), 6.82 (t, 2H, J = 2.3 Hz), 6.58 (d, 2H, J = 9.3 Hz), 6.11 (t, 2H, J = 2.3 Hz), 4.41 (sept, 1H, J = 5.8 Hz), 1.18 (d, 6H, J = 5.8 Hz). LCMS: ret. time: 21.21 min.; purity: 90%; MS (m/e): 328 (MH⁺).

7.3.1030 N2-(3, 4-Ethylenedioxyphenyl)-5-Fluoro-N4-(1H-pyrrol-1-yl)- 2,4-pyrimidinediamine (R935277)

In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N-(1H-pyrrol-1-yl)-4-pyrimidineamine was reacted with 3, 4-ethylenedioxyaniline to produce N2-(3, 4-ethylenedioxyphenyl)-5-Fluoro-N4-(1H-pyrrol-1-yl)- 2,4-pyrimidinediamine. ¹H NMR (DMSO-d₆): δ 11.63 (s, 1H), 9.94 (s, 1H), 8.23 (d, 1H, J = 4.7 Hz), 6.86 (m, 4H), 6.58 (d, 1H, J = 8.8 Hz), 6.12 (t, 2H, J = 2.3 Hz), 4.15 (s, 4H). LCMS: ret. time: 17.36 min.; purity: 96%; MS (m/e): 328 (MH⁺).

7.3.1031 5-Fluoro-N2-(3-hydroxyphenyl)-N4-(1H-pyrrol-1-yl)- 2,4-pyrimidinediamine (R935278)

In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N-(1H-pyrrol-1-yl)-4-pyrimidineamine was reacted with 3-aminophenol to produce 5-fluoro-N2-(3-hydroxyphenyl)-N4-(1H-pyrrol-1-yl)- 2,4-pyrimidinediamine. ¹H NMR (DMSO-d₆): δ 10.68 (s, 1H), 9.04 (s, 1H), 9.00 (s, 1H), 8.08 (d, 1H, J = 4.11 Hz), 7.01 (d, 1H, J = 8.2

Hz), 6.84-6.75 (m, 4H), 6.22 (dd, 1H, $J = 1.2$ and 8.2 Hz), 6.08 (t, 2H, $J = 2.3$ Hz). LCMS: ret. time: 16.24 min.; purity: 94%; MS (m/e): 286 (MH^+).

7.3.1032 5-Fluoro-N4-(indazoline-5-yl)-N2-[3-(*N*-methylaminocarbonylmethyleneoxy)phenyl]-2,4-pyrimidinediamine (R935279)

In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(*N*-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, 5-fluoro-N4-(indazoline-5-yl)-N2-[3-(*N*-methoxycarbonylmethyleneoxy)phenyl]-2,4-pyrimidinediamine and $Me_2NH \cdot HCl$ were reacted to provide 5-fluoro-N4-(indazoline-5-yl)-N2-[3-(*N*-methylaminocarbonylmethyleneoxy)phenyl]-2,4-pyrimidinediamine. 1H NMR ($DMSO-d_6$): δ 12.98 (s, 1H), 9.35 (s, 1H), 9.16 (s, 1H), 8.21 (s, 1H), 8.07 (d, 1H, $J = 3.5$ Hz), 7.97 (s, 1H), 7.90 (qt, 1H, $J = 4.7$ Hz), 7.59 (dd, 1H, $J = 8.8$ Hz), 7.49 (d, 1H, $J = 8.8$ Hz), 7.32-7.28 (m, 2H), 7.03 (t, 1H, $J = 8.2$ Hz), 6.45 (dd, 1H, $J = 1.7$ and 8.2 Hz), 4.31 (s, 2H), 2.61 (d, 3H, $J = 4.7$ Hz). LCMS: ret. time: 12.92 min.; purity: 90%; MS (m/e): 408 (MH^+).

7.3.1033 5-Fluoro-N2-[3-(methoxycarbonylmethyleneoxy)phenyl]-N4-(1H-pyrrol-1-yl)-2,4-pyrimidinediamine (R935280)

In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N-(1H-pyrrol-1-yl)-4-pyrimidineamine was reacted with 3-(methoxycarbonylmethyleneoxy)aniline to produce 5-fluoro-N2-[3-(methoxycarbonylmethyleneoxy)phenyl]-N4-(1H-pyrrol-1-yl)-2,4-pyrimidinediamine. 1H NMR ($DMSO-d_6$): δ 11.45(s, 1H), 9.90 (s, 1H), 8.26 (d, 1H, $J = 4.7$ Hz), 7.07 (d, 1H, $J = 8.2$ Hz), 7.68 (d, 1H, $J = 8.2$ Hz), 6.94 (s, 1H), 6.85 (t, 2H, $J = 2.3$ Hz), 6.47 (dd, 1H, $J = 2.3$ and 8.2 Hz), 6.12 (t, 2H, $J = 2.3$ Hz), 4.64 (s, 2H), 3.68 (s, 3H). LCMS: ret. time: 16.24 min.; purity: 92%; MS (m/e): 358 (MH^+).

7.3.1034 5-Fluoro-N2-[3-(*N*-methylaminocarbonylmethyleneoxy)phenyl]-N4-(1H-pyrrol-1-yl)-2,4-pyrimidinediamine (R935281)

In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(*N*-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, 5-fluoro-N2-[3-(*N*-methoxycarbonylmethyleneoxy)phenyl]-N4-(1H-pyrrol-1-yl)-2,4-pyrimidinediamine and $Me_2NH \cdot HCl$ were reacted to provide 5-fluoro-N2-[3-(*N*-methylaminocarbonylmethyleneoxy)phenyl]-N4-(1H-pyrrol-1-yl)-2,4-pyrimidinediamine. 1H NMR ($DMSO-d_6$): δ 10.73 (s, 1H), 9.21 (s, 1H), 8.11 (d, 1H, $J = 4.1$ Hz), 7.89 (qt, 1H, J

= 4.7 Hz), 7.14 (d, 1H, J = 8.2 Hz), 7.09 (s, 1H), 6.93 (t, 1H, J = 8.2 Hz), 6.84 (t, 2H, J = 2.3 Hz), 6.40 (dd, 1H, J = 2.3 and 8.2 Hz), 6.09 (t, 2H, J = 2.3 Hz), 4.29 (s, 2H), 2.63 (s, 3H, J = 4.7 Hz). LCMS: ret. time: 16.16 min.; purity: 90%; MS (*m/e*): 357 (MH⁺).

7.3.1035 N2-[1-(2-ethoxycarbonylethyl)indazoline-6-yl]- N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R935286)

In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N-(3, 4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine was reacted with 6-amino-1-(2-ethoxycarbonylethyl)indazoline to provide N2-[1-(2-ethoxycarbonylethyl)indazoline-6-yl]- N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine. ¹H NMR (DMSO-d₆): δ 9.37 (s, 1H), 9.20 (s, 1H), 8.10 (d, 1H, J = 3.5 Hz), 8.06 (s, 1H), 7.87 (s, 1H), 7.53 (d, 1H, J = 8.8 Hz), 7.33-7.21 (m, 3H), 6.77 (d, 1H, J = 8.8 Hz), 4.34 (t, 2H, J = 6.4 Hz), 4.19 (s, 4H), 3.93 (qt, 2H, J = 7.0 Hz), 2.82 (t, 2H, J = 6.4 Hz), 1.04 (t, 3H, J = 7.0 Hz). LCMS: ret. time: 24.70 min.; purity: 90%; MS (*m/e*): 479 (MH⁺).

7.3.1036 N4-(3, 4-Ethylenedioxyphenyl)-5-fluoro-N2-[1-(3-hydroxypropyl)indazoline-6-yl]-2,4-pyrimidinediamine (R935287)

In like manner to the preparation of N2-(3, 4-ethylenedioxyphenyl)-5-fluoro-N4-[4(2-hydroxy-1,1-dimethylethyl)phenyl]-2,4-pyrimidinediamine, N2-[1-(2-ethoxycarbonylethyl)indazoline-6-yl]- N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine was reacted with DIBAL-H to produce N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-[1-(3-hydroxypropyl)indazoline-6-yl]-2,4-pyrimidinediamine. ¹H NMR (DMSO-d₆): δ 9.35 (s, 1H), 9.19 (s, 1H), 8.09 (d, 1H, J = 4.1 Hz), 8.01 (s, 1H), 7.85 (s, 1H), 7.53 (d, 1H, J = 8.8 Hz), 7.32-7.20 (m, 3H), 6.77 (d, 1H, J = 8.8 Hz), 4.20 (s, 4H), 3.27 (t, 2H, J = 6.4 Hz), 3.27 (t, 2H, J = 6.4 Hz), 1.84 (q, 2H, J = 6.4 Hz). LCMS: ret. time: 24.70 min.; purity: 90%; MS (*m/e*): 479 (MH⁺). LCMS: ret. time: 22.09 min.; purity: 90%; MS (*m/e*): 437 (MH⁺).

7.3.1037 N2-(3, 4-Ethylenedioxyphenyl)-5-fluoro-N4-[1-[2(*N*-methylaminocarbonyl)ethyl]-indazoline-6-yl]-2,4-pyrimidinediamine (R935288)

In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(*N*-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, N2-[1-(2-

ethoxycarbonyl)ethyl]indazoline-6-yl]-N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine and Me₂NH.HCl were reacted to provide N2-(3, 4-ethylenedioxyphenyl)-5-fluoro-N4-[1-[2(*N*-methylaminocarbonyl)ethyl]-indazoline-6-yl]-2,4-pyrimidinediamine. ¹H NMR (DMSO-d₆): δ 9.35 (s, 1H), 9.19 (s, 1H), 8.10 (d, 1H, J = 3.5 Hz), 8.02 (s, 1H), 7.86 (s, 1H), 7.81 (qt, 1H, J = 4.7 Hz), 7.52 (d, 1H, J = 8.2 Hz), 7.34-7.22 (m, 3H), 6.77 (d, 1H, J = 8.8 Hz), 4.33 (t, 2H, J = 6.4 Hz), 4.19 (s, 4H), 2.57 (t, 2H, J = 6.4 Hz), 2.48 (d, 3H, J = 4.7 Hz). LCMS: ret. time: 23.10 min.; purity: 93%; MS (*m/e*): 464 (MH⁺).

7.3.1038 N4-[1-(2-Ethoxycarbonyl)ethyl]indazoline-6-yl]- 5-fluoro-N2-(isopropoxyphenyl)-2,4-pyrimidinediamine (R935289)

In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N-(4-isopropoxyphenyl)-4-pyrimidineamine was reacted with 6-amino-1-(2-ethoxycarbonyl)ethylindazoline to provide N2-[1-(2-ethoxycarbonyl)ethyl]indazoline-6-yl]- 5-fluoro-N4-(isopropoxyphenyl)-2,4-pyrimidinediamine. ¹H NMR (DMSO-d₆): δ 10.74 (s, 1H), 10.55 (s, 1H), 8.35 (d, 1H, J = 5.8 Hz), 7.98 (s, 1H), 7.77 (s, 1H), 7.66 (d, 1H, J = 8.8 Hz), 7.51 (d, 2H, J = 8.8 Hz), 7.16 (dd, 1H, J = 1.2 and 8.8 Hz), 6.85 (d, 2H, J = 8.8 Hz), 4.55 (sept, 1H, J = 6.4 Hz), 4.31 (t, 2H, J = 6.4 Hz), 3.93 (qt, 2H, J = 7.0 Hz), 2.80 (t, 2H, J = 6.4 Hz), 1.22 (d, 6H, J = 7.0 Hz), 1.02 (t, 3H, J = 7.0 Hz). LCMS: ret. time: 26.84 min.; purity: 96%; MS (*m/e*): 479 (MH⁺).

7.3.1039 5-Fluoro-N2-[1-(3-hydroxypropyl)indazoline-6-yl]-N4-(4-isopropoxyphenyl)-2,4-pyrimidinediamine (R935290)

In like manner to the preparation of N2-(3, 4-ethylenedioxyphenyl)-5-fluoro-N4-[4(2-hydroxy-1,1-dimethylethyl)phenyl]-2,4-pyrimidinediamine, N2-[1-(2-ethoxycarbonyl)ethyl]indazoline-6-yl]- 5-fluoro-N4-(isopropoxyphenyl)-2,4-pyrimidinediamine was reacted with DIBAL-H to produce 5-fluoro-N2-[1-(3-hydroxypropyl)indazoline-6-yl]-N4-(4-isopropoxyphenyl)-2,4-pyrimidinediamine. ¹H NMR (DMSO-d₆): δ 9.31 (s, 1H), 9.22 (s, 1H), 8.08 (d, 1H, J = 4.1 Hz), 7.98 (s, 1H), 7.85 (s, 1H), 7.62 (dd, 2H, J = 3.5 and 8.8 Hz), 7.52 (d, 1H, J = 8.8 Hz), 7.27 (d, 1H, J = 8.8 Hz), 6.86 (d, 2H, J = 8.8 Hz), 4.55 (sept, 1H, J = 7.0 Hz), 4.49 (t, 1H, J = 5.3 Hz), 4.14 (t, 2H, J = 6.4 Hz), 3.26 (t, 2H, J = 6.4 Hz), 1.84 (q, 2H, J = 6.4 Hz), 1.24 (d, 6H, J = 7.0 Hz). LCMS: ret. time: 24.13 min.; purity: 97%; MS (*m/e*): 437 (MH⁺).

7.3.1040 5-Fluoro-N4-(4-isopropoxyphenyl)-N2-[1-[2(*N*-methylamino)carbonyl]ethyl-indazoline-6-yl]-2,4-pyrimidinediamine (R935291)

In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(*N*-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, N2-[1-(2-ethoxycarbonyl)ethyl]indazoline-6-yl]- 5-fluoro-N4-(isopropoxyphenyl)-2,4-pyrimidinediamine and Me₂NH.HCl were reacted to provide 5-fluoro-N4-(4-isopropoxyphenyl)-N2-[1-[2(*N*-methylamino)carbonyl]ethyl-indazoline-6-yl]-2,4-pyrimidinediamine. ¹H NMR (DMSO-d₆): δ 9.32(s, 1H), 9.24 (s, 1H), 8.10 (d, 1H, J = 3.5 Hz), 7.99 (s, 1H), 7.85 (s, 1H), 7.80 (qt, 1H, J = 4.7 Hz), 7.63 (d, 2H, J = 8.8 Hz), 7.52 (d, 1H, J = 8.8 Hz), 7.28 (d, 1H, J = 8.8 Hz), 6.84 (d, 2H, J = 8.8 Hz), 4.54 (sept, 1H, J = 5.8 Hz), 4.30 (t, 2H, J = 6.4 Hz), 2.55 (t, 2H, 7.4 Hz), 2.48 (d, 3H, J = 4.7 Hz), 1.24 (d, 6H, J = 6H). LCMS: ret. time: 23.68 min.; purity: 95%; MS (*m/e*): 464 (MH⁺).

7.3.1041 N4-[1-(2-Ethoxycarbonyl)ethyl]indazoline-6-yl]- 5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine (R935292)

In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N-(3-hydroxyphenyl)-4-pyrimidineamine was reacted with 6-amino-1-(2-ethoxycarbonyl)ethylindazoline to provide N4-[1-(2-ethoxycarbonyl)ethyl]indazoline-6-yl]- 5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine. ¹H NMR (DMSO-d₆): δ 10.35 (s, 1H), 10.21 (s, 1H), 8.29 (d, 1H, J = 5.3 Hz), 7.96 (s, 1H), 7.90 (s, 1H), 7.63 (d, 1H, J = 8.8 Hz), 7.20-7.06 (m, 4H), 6.58 (d, 1H, J = 8.2 Hz), 4.33 (t, 2H, J = 6.4 Hz), 3.94 (qt, 2H, J = 7.0 Hz), 2.82 (t, 2H, J = 6.4 Hz), 1.03 (t, 3H, J = 7.0 Hz). LCMS: ret. time: 22.73 min.; purity: 94%; MS (*m/e*): 437 (MH⁺).

7.3.1042 5-Fluoro-N4-(3-hydroxyphenyl)-N2-[1-(3-hydroxypropyl)indazoline-6-yl]-2,4-pyrimidinediamine (R935293)

In like manner to the preparation of N2-(3, 4-ethylenedioxyphenyl)-5-fluoro-N4-[4(2-hydroxy-1,1-dimethylethyl)phenyl]-2,4-pyrimidinediamine, N4-[1-(2-ethoxycarbonyl)ethyl]indazoline-6-yl]- 5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine was reacted with DIBAL-H to produce 5-fluoro-N4-(3-hydroxyphenyl)-N2-[1-(3-hydroxypropyl)indazoline-6-yl]-2,4-pyrimidinediamine. ¹H NMR (DMSO-d₆): δ 9.38 (s, 1H), 9.35 (s, 1H), 9.26 (s, 1H), 8.13 (d, 1H, J = 4.1 Hz), 8.05 (s, 1H), 7.85 (s, 1H), 7.52 (d, 1H, J = 8.2 Hz), 7.28 (d, 2H, J = 8.8 Hz), 7.12 (d, 1H, J = 1.7 Hz), 7.08 (t, 1H, J =

8.2 Hz), 6.49 (d, 1H, J = 8.2 Hz), 4.15 (t, 2H, J = 7.0 Hz), 3.26 (t, 2H, J = 6.4 Hz), 1.85 (q, 2H, J = 6.4 Hz). LCMS: ret. time: 24.70 min.; purity: 90%; MS (*m/e*): 479 (MH⁺). LCMS: ret. time: 20.37 min.; purity: 98%; MS (*m/e*): 395 (MH⁺).

7.3.1043 5-Fluoro-N4-(3-hydroxyphenyl)-N2-[1-[2-(*N*-methylaminocarbonyl)ethyl]-indazoline-6-yl]-2,4-pyrimidinediamine (R935294)

In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(*N*-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, N4-[1-(2-ethoxycarbonyl)ethyl]indazoline-6-yl]- 5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine and Me₂NH.HCl were reacted to provide 5-fluoro-N4-(3-hydroxyphenyl)-N2-[1-[2-(*N*-methylaminocarbonyl)ethyl]-indazoline-6-yl]-2,4-pyrimidinediamine. ¹H NMR (DMSO-d₆): δ 9.36 (s, 1H), 9.33 (s, 1H), 9.25 (s, 1H), 8.14 (d, 1H, J = 3.5 Hz), 8.05 (s, 1H), 7.85 (s, 1H), 7.78 (qt, 1H, J = 4.7 Hz), 7.52 (d, 1H, J = 8.8 Hz), 7.30 (d, 2H, J = 8.8 Hz), 7.11 (d, 1H, J = 2.3 Hz), 7.07 (t, 1H, J = 8.2 Hz), 6.47 (d, 1H, J = 8.2 Hz), 4.32 (t, 2H, J = 6.4 Hz), 2.57 (t, 2H, J = 6.4 Hz), 2.48 (d, 3H, J = 4.7 Hz). LCMS: ret. time: 20.18 min.; purity: 93%; MS (*m/e*): 422 (MH⁺).

7.3.1044 N4-[1-(2-Ethoxycarbonyl)ethyl]indazoline-6-yl]- 5-fluoro-N2-(2-methoxycarbonylbenzofur-5-yl)-2,4-pyrimidinediamine (R935295)

In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N-(2-methoxycarbonylbenzofur-5-yl)-4-pyrimidineamine was reacted with 6-amino-1-(2-ethoxycarbonyl)ethylindazoline to provide N4-[1-(2-ethoxycarbonyl)ethyl]indazoline-6-yl]- 5-fluoro-N2-(2-methoxycarbonylbenzofur-5-yl)-2,4-pyrimidinediamine Purification of the crude gave two products.

N4-[1-(2-Ethoxycarbonyl)ethyl]indazoline-6-yl]- 5-fluoro-N2-(2-methoxycarbonylbenzofur-5-yl)-2,4-pyrimidinediamine (R935295):

¹H NMR (DMSO-d₆): δ 9.54 (s, 1H), 9.41 (s, 1H), 8.21 (app d, 1H, J = 1.7 Hz), 8.17 (d, 1H, J = 3.5 Hz), 8.01 (s, 1H), 7.86 (s, 1H), 7.83-7.80 (m 2H), 7.68 (d, 1H, J = 8.8 Hz), 7.59 (s, 1H), 7.52 (d, 1H, J = 8.2 Hz), 7.25 (d, 1H, J = 8.2 Hz), 4.12 (t, 2H, J = 6.4 Hz), 3.91 (qt, 2H, J = 7.0 Hz), 3.88 (s, 3H), 2.72 (t, 2H, J = 6.4 Hz), 1.02 (t, 3H, J = 7.0 Hz). LCMS: ret. time: 25.67 min.; purity: 91%; MS (*m/e*): 519 (MH⁺) and

N4-[1-(2-carboxyethyl)indazoline-6-yl]- 5-fluoro-N2-(2-methoxycarbonylbenzofur-5-yl)-2,4-pyrimidinediamine (R935296)

¹H NMR (DMSO-d₆): δ 9.54 (s, 1H), 9.39 (s, 1H), 8.23 (app d, 1H, J = 1.7 Hz), 8.17 (d, 1H, J = 3.5 Hz), 8.00 (s, 1H), 7.86 (s, 1H), 7.83-7.80 (m 2H), 7.68 (d, 1H, J = 8.8 Hz), 7.58 (s, 1H), 7.52 (d, 1H, J = 8.2 Hz), 7.28 (d, 1H, J = 8.2 Hz), 4.13 (t, 2H, J = 6.4 Hz), 3.88 (s, 3H), 2.67 (t, 2H, J = 6.4 Hz). LCMS: ret. time: 23.28 min.; purity: 91%; MS (*m/e*): 491 (MH⁺).

7.3.1045 5-Fluoro-N4-[2-(*N*-methylaminocarbonyl)benzofuran-5-yl]-N2-[1-[2(*N*-methylaminocarbonyl)ethyl]-indazoline-6-yl]-2,4-pyrimidinediamine (R935297)

In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(*N*-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, N4-[1-(2-ethoxycarbonyl)ethyl]indazoline-6-yl]- 5-fluoro-N2-(2-methoxycarbonylbenzofur-5-yl)-2,4-pyrimidinediamine and Me₂NH.HCl were reacted to provide 5-fluoro-N4-[2-(*N*-methylaminocarbonyl)benzofuran-5-yl]-N2-[1-[2(*N*-methylaminocarbonyl)ethyl]-indazoline-6-yl]-2,4-pyrimidinediamine. ¹H NMR (DMSO-d₆): δ 10.00 (s, 1H), 9.90 (s, 1H), 8.70 (qt, 1H, J = 4.7 Hz), 8.24 (d, 1H, J = 4.1 Hz), 8.12 (d, 1H, J = 1.7 Hz), 7.911 (s, 1H), 7.86 (s, 1H), 7.81 (qt, 1H, J = 4.7 Hz), 7.71 (d, 2H, J = 1.7 and 8.8 Hz), 7.57 (dd, 1H, J = 3.5 and 8.8 Hz), 7.35 (s, 1H), 7.26 (dd, 1H, J = 3.5 and 8.8 Hz), 4.19 (t, 2H, J = 7.0 Hz), 2.53 (t, 2H, J = 7.0 Hz), 2.47 (d, 6H, J = 4.7 Hz). LCMS: ret. time: 20.18 min.; purity: 89%; MS (*m/e*): 503 (MH⁺).

7.3.1046 5-Fluoro-N4-(4-isopropoxyphenyl)-N2-(2-methyl-indazoline-5-yl)-2,4-pyrimidinediamine (R935298)

In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N-(4-isopropoxyphenyl)-4-pyrimidineamine and 5-amino-2-methylindazoline were reacted to give 5-fluoro-N4-(4-isopropoxyphenyl)-N2-(2-methyl-indazoline-5-yl)-2,4-pyrimidinediamine. ¹H NMR (DMSO-d₆): δ 9.15 (s, 1H), 9.03 (s, 1H), 8.03-8.00 (m, 3H), 7.60 (dd, 2H, J = 4.1 and 8.8 Hz), 7.42 (d, 1H, J = 9.3 Hz), 7.31 (d, 1H, J = 9.3 Hz), 6.86 (d, 2H, J = 8.8 Hz), 4.57 (sept, 1H, J = 6.4 Hz), 4.08 (s, 3H), 1.26 (d, 6H, J = 6.4 Hz), LCMS: ret. time: 23.89 min.; purity: 98%; MS (*m/e*): 393 (MH⁺).

7.3.1047 5-Fluoro-N4-(3-hydroxyphenyl)-N2-(2-methy-indazoline-5-yl)-2,4-pyrimidinediamine (R935299)

In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N-(3-hydroxyphenyl)-4-pyrimidineamine was reacted with 5-amino-2-methylindazoline to produce 5-fluoro-N4-(3-hydroxyphenyl)-N2-(2-methy-indazoline-5-yl)-2,4-pyrimidinediamine. ¹H NMR (DMSO-d₆): δ 10.35 (s, 1H), 10.30 (s, 1H), 9.62 (br s, 1H), 8.22 (d, 1H, J = 5.3 Hz), 8.13 (s, 1H), 7.85 (s, 1H), 7.49 (d, 1H, J = 8.8 Hz), 7.17 (dd, 1H, J = 1.7 and 9.3 Hz), 7.08 (d, 2H, J = 5.3 Hz), 7.03 (s, 1H), 6.64-6.60 (m, 1H), 4.09 (s, 3H). LCMS: ret. time: 20.01 min.; purity: 97%; MS (*m/e*): 351 (MH⁺).

7.3.1048 N4-(3, 4-Ethylenedioxyphenyl)-5-fluoro-N2-(2-methy-indazoline-5-yl)-2,4-pyrimidinediamine (R935300)

In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N-(3, 4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine was reacted with 5-amino-2-methylindazoline to produce N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(2-methy-indazoline-5-yl)-2,4-pyrimidinediamine. ¹H NMR (DMSO-d₆): δ 10.64 (s, 1H), 10.62 (s, 1H), 8.22 (d, 1H, J = 5.3 Hz), 8.21 (s, 1H), 7.77 (s, 1H), 7.58 (d, 1H, J = 9.3 Hz), 7.23-7.19 (m, 2H), 7.10 (dd, 1H, J = 2.3 and 8.8 Hz), 6.78 (d, 1H, J = 8.8 Hz), 4.21 (s, 3H), 4.15 (s, 4H). LCMS: ret. time: 21.77 min.; purity: 92%; MS (*m/e*): 393 (MH⁺).

7.3.1049 N2-[1-(2-Ethoxycarbonylethyl)indazoline-5-yl]- N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R935301)

In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N-(3, 4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine was reacted with 5-amino-1-(2-ethoxycarbonylethyl)indazoline to provide N2-[1-(2-ethoxycarbonylethyl)indazoline-5-yl]- N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine. ¹H NMR (DMSO-d₆): δ 9.15 (s, 1H), 9.13 (s, 1H), 8.10, (s, 1H), 8.04 (d, 1H, J = 3.5 Hz), 7.83 (s, 1H), 7.50 (s, 2H), 7.30 (d, 1H, J = 2.3 and 8.8 Hz), 6.79 (d, 1H, J = 8.8 Hz), 4.55 (t, 2H, J = 6.4 Hz), 4.22 (s, 4H), 3.97 (qt, 2H, J = 7.0 Hz), 2.88 (t, 2H, J = 6.4 Hz), 1.06 (t, 3H, J = 7.0 Hz). LCMS: ret. time: 25.19 min.; purity: 93%; MS (*m/e*): 479 (MH⁺).

7.3.1050 N4-(3, 4-Ethylenedioxyphenyl)-5-fluoro-N2-[1-(3-hydroxypropyl)indazoline-5-yl]-2,4-pyrimidinediamine (R935302)

In like manner to the preparation of N2-(3, 4-ethylenedioxyphenyl)-5-fluoro-N4-[4(2-hydroxy-1,1-dimethylethyl)phenyl]-2,4-pyrimidinediamine, N2-[1-(2-ethoxycarbonylethyl)indazoline-5-yl]- N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine was reacted with DIBAL-H to produce N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-[1-(3-hydroxypropyl)indazoline-5-yl]-2,4-pyrimidinediamine. ¹H NMR (DMSO-d₆): δ 9.14 (s, 1H), 9.13 (s, 1H), 8.09 (s, 1H), 8.03 (d, 1H, J = 4.1 Hz), 7.82 (s, 1H), 7.48 (s, 2H), 7.30 (d, 1H, J = 2.3 Hz), 7.18 (dd, 1H, J = 2.3 and 8.8 Hz), 6.78 (d, 1H, J = 8.8 Hz), 4.59 (t, 1H, J = 6.4 Hz), 4.37 (t, 2H, J = 6.4 Hz), 4.22 (s, 4H), 3.34 (t, 2H, J = 6.4 Hz), 1.84 (q, 2H, J = 6.4 Hz). LCMS: ret. time: 22.33 min.; purity: 100%; MS (*m/e*): 437 (MH⁺).

7.3.1051 N4-[1-(2-Ethoxycarbonylethyl)indazoline-5-yl]- 5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine (R935303)

In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N-(3-hydroxyphenyl)-4-pyrimidineamine was reacted with 5-amino-1-(2-ethoxycarbonylethyl)indazoline to provide N4-[1-(2-ethoxycarbonylethyl)indazoline-5-yl]- 5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine. ¹H NMR (DMSO-d₆): δ 10.50 (s, 1H), 10.46 (s, 1H), 9.62 (br s 1H), 8.28 (d, 1H, J = 5.8 Hz), 7.96 (s, 2H), 7.65 (d, 1H, J = 8.8 Hz), 7.36 (dd, 1H, J = 1.7 and 8.8 Hz), 7.15-7.08 (m, 3H), 6.67-6.64 (m, 1H), 4.59 (t, 2H, J = 6.4 Hz), 3.97 (qt, 2H, J = 7.0 Hz), 2.89 (t, 2H, J = 6.4 Hz), 1.06 (t, 3H, J = 7.0 Hz). LCMS: ret. time: 23.68 min.; purity: 97%; MS (*m/e*): 437 (MH⁺).

7.3.1052 5-Fluoro-N4-(3-hydroxyphenyl)-N2-[1-(3-hydroxypropyl)indazoline-5-yl]-2,4-pyrimidinediamine (R935304)

In like manner to the preparation of N2-(3, 4-ethylenedioxyphenyl)-5-fluoro-N4-[4(2-hydroxy-1,1-dimethylethyl)phenyl]-2,4-pyrimidinediamine, N4-[1-(2-ethoxycarbonylethyl)indazoline-5-yl]- 5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine was reacted with DIBAL-H to produce 5-fluoro-N4-(3-hydroxyphenyl)-N2-[1-(3-hydroxypropyl)indazoline-5-yl]-2,4-pyrimidinediamine. ¹H NMR (DMSO-d₆): δ 9.39 (s, 1H), 9.18 (s, 1H), 9.15 (s, 1H), 8.20 (s, 1H), 8.07 (d, 1H, J = 4.1 Hz), 7.84 (s, 1H), 7.46 (s, 2H), 7.24 (d, 1H, J = 8.2 Hz), 7.11-7.06 (m, 2H), 6.53 (d, 1H, J = 8.8 Hz), 4.56 (t,

1H, J = 4.7 Hz), 4.37 (t, 2H, J = 6.4 Hz), 3.34 (t, 2H, J = 6.4 Hz), 1.92 (q, 2H, J = 6.4 Hz). LCMS: ret. time: 24.70 min.; purity: 90%; MS (*m/e*): 479 (MH⁺). LCMS: ret. time: 20.89 min.; purity: 98%; MS (*m/e*): 395 (MH⁺).

7.3.1053 5-Fluoro-N4-(3-hydroxyphenyl)-N2-[1-[2(*N*-methylaminocarbonyl)ethyl]-indazoline-5-yl]-2,4-pyrimidinediamine (R935305)

In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(*N*-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, N4-[1-(2-ethoxycarbonyl)ethyl]indazoline-5-yl]- 5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine and Me₂NH.HCl were reacted to provide 5-fluoro-N4-(3-hydroxyphenyl)-N2-[1-[2(*N*-methylaminocarbonyl)ethyl]-indazoline-5-yl]-2,4-pyrimidinediamine. ¹H NMR (DMSO-d₆): δ 9.39 (s, 1H), 9.18 (s, 1H), 9.15 (s, 1H), 8.19 (s, 1H), 8.06 (d, 1H, J = 3.5 Hz), 7.84 (s, 1H), 7.82 (qt, 1H, J = 4.7 Hz), 7.46 (t, 2H, J = 8.2 Hz), 7.25 (d, 1H, J = 8.2 Hz), 7.11 (d, 1H, J = 8.2 Hz), 7.10 (d, 1H, J = 8.2 Hz), 6.53 (t, 1H, J = 8.2 Hz), 4.51 (t, 2H, J = 7.0 Hz), 2.61 (t, 2H, J = 7.0 Hz), 2.49 (d, 3H, J = 4.7 Hz). LCMS: ret. time: 20.66 min.; purity: 95%; MS (*m/e*): 422 (MH⁺).

7.3.1054 N4-[1-(2-Ethoxycarbonyl)ethyl]indazoline-5-yl]- 5-fluoro-N2-(4-isopropoxyphenyl)-2,4-pyrimidinediamine (R935306)

In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N-(4-isopropoxyphenyl)-4-pyrimidineamine was reacted with 5-amino-1-(2-ethoxycarbonyl)ethylindazoline to provide N2-[1-(2-ethoxycarbonyl)ethyl]indazoline-5-yl]- 5-fluoro-N4-(4-isopropoxyphenyl)-2,4-pyrimidinediamine. ¹H NMR (DMSO-d₆): δ 10.48 (s, 1H), 10.41 (s, 1H), 8.25 (d, 1H, J = 5.8 Hz), 7.93 (s, 1H), 7.84 (s, 1H), 7.66 (d, 1H, J = 8.8 Hz), 7.49 (d, 2H, J = 8.8 Hz), 7.36 (dd, 1H, J = 2.3 and 8.8 Hz), 6.86 (d, 2H, J = 8.8 Hz), 4.59 (t, 2H, J = 6.4 Hz), 4.57 (sept, 1H, J = 7.0 Hz), 3.96 (qt, 2H, J = 7.0 Hz), 2.89 (t, 2H, J = 6.4 Hz), 1.23 (d, 6H, J = 7.0 Hz), 1.05 (t, 3H, J = 7.0 Hz). LCMS: ret. time: 27.39 min.; purity: 98%; MS (*m/e*): 479 (MH⁺).

7.3.1055 5-Fluoro-N2-[1-(3-hydroxypropyl)indazoline-5-yl]-N4-(4-isopropoxyphenyl)-2,4-pyrimidinediamine (R935307)

In like manner to the preparation of N2-(3, 4-ethylenedioxyphenyl)-5-fluoro-N4-[4(2-hydroxy-1,1-dimethylethyl)phenyl]-2,4-pyrimidinediamine, N2-[1-(2-ethoxycarbonyl)ethyl]indazoline-5-yl]- 5-fluoro-N4-(4-isopropoxyphenyl)-2,4-

pyrimidinediamine was reacted with DIBAL-H to produce 5-fluoro-N2-[1-(3-hydroxypropyl)indazoline-5-yl]-N4-(4-isopropoxyphenyl)-2,4-pyrimidinediamine. ¹H NMR (DMSO-d₆): δ 9.16 (s, 1H), 9.10 (s, 1H), 8.09 (s, 1H), 8.03 (d, 1H, J = 4.1 Hz), 7.79 (s, 1H), 7.57 (d, 2H, J = 8.8 Hz), 7.46 (t, 2H), 6.87 (d, 2H, J = 8.8 Hz), 4.60-4.52 (m, 2H), 4.37 (t, 2H, J = 6.4 Hz), 3.34 (t, 2H, J = 6.4 Hz), 1.84 (q, 2H, J = 6.4 Hz), 1.24 (d, 6H, J = 7.0 Hz). LCMS: ret. time: 23.71 min.; purity: 98%; MS (*m/e*): 437 (MH⁺).

7.3.1056 5-Fluoro-N4-(2-hydroxymethylbenzofur-5-yl)- N2-[1-(3-hydroxypropyl)indazoline-6-yl]- 2,4-pyrimidinediamine (R935308)

In like manner to the preparation of N2-(3, 4-ethylenedioxyphenyl)-5-fluoro-N4-[4(2-hydroxy-1,1-dimethylethyl)phenyl]-2,4-pyrimidinediamine, N4-[1-(2-ethoxycarbonyl)ethyl]indazoline-6-yl]- 5-fluoro-N2-(2-methoxycarbonylbenzofur-5-yl)-2,4-pyrimidinediamine was reacted with DIBAL-H to produce 5-fluoro-N4-(2-hydroxymethylbenzofur-5-yl)- N2-[1-(3-hydroxypropyl)indazoline-6-yl]- 2,4-pyrimidinediamine. ¹H NMR (DMSO-d₆): δ 9.35 (s, 1H), 9.33 (s, 1H), 8.12 (d, 1H, J = 3.5 Hz), 7.99 (d, 1H, J = 1.7 Hz), 7.95 (s, 1H), 7.84 (s, 1H), 7.55-7.49 (m, 3H), 7.28 (d, 1H, J = 8.8 Hz), 6.62 (s, 1H), 5.46 (t, 1H, J = 5.8 Hz), 4.55 (d, 2H, J = 5.8 Hz), 4.45 (t, 1H, J = 4.7 Hz), 3.96 (t, 2H, J = 6.4 Hz), 3.20 (t, 2H, J = 6.4 Hz), 1.76 (q, 2H, J = 6.4 Hz). LCMS: ret. time: 20.86 min.; purity: 99%; MS (*m/e*): 449 (MH⁺).

7.3.1057 N4-(3, 4-Ethylenedioxyphenyl)-5-fluoro-N2-[1-[2(*N*-methylaminocarbonyl)ethyl]-indazoline-5-yl]-2,4-pyrimidinediamine (R935309)

In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(*N*-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, N4-[1-(2-ethoxycarbonyl)ethyl]indazoline-5-yl]- N2-(3, 4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine and Me₂NH.HCl were reacted to provide N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-[1-[2(*N*-methylaminocarbonyl)ethyl]-indazoline-5-yl]-2,4-pyrimidinediamine. ¹H NMR (DMSO-d₆): δ 9.12 (s, 1H), 9.11 (s, 1H), 8.09 (s, 1H), 8.03 (d, 1H, J = 3.5 Hz), 7.82 (s, 2H), 7.47 (s, 2H), 7.32-7.30 (m, 1H), 7.22-7.17 (m, 1H), 6.80 (d, 1H, J = 8.8 Hz), 4.51 (t, 2H, J = 7.0 Hz), 4.22 (s, 4H), 2.62 (t, 2H, J = 7.0 Hz), 2.49 (d, 3H, J = 4.7 Hz). LCMS: ret. time: 18.67 min.; purity: 100%; MS (*m/e*): 464 (MH⁺).

7.3.1058 5-Fluoro-N4-(4-isopropoxyphenyl)-N2-[1-[2(*N*-methylaminocarbonyl)ethyl]-indazoline-5-yl]-2,4-pyrimidinediamine (R935310)

In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(*N*-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, N2-[1-(2-ethoxycarbonyl)ethyl]indazoline-5-yl]- 5-fluoro-N4-(4-isopropoxyphenyl)-2,4-pyrimidinediamine and Me₂NH.HCl were reacted to provide 5-fluoro-N4-(4-isopropoxyphenyl)-N2-[1-[2(*N*-methylaminocarbonyl)ethyl]indazoline-5-yl]-2,4-pyrimidinediamine. ¹H NMR (DMSO-d₆): δ 9.18 (s, 1H), 9.09 (s, 1H), 8.08 (s, 1H), 8.02 (d, 1H, J = 4.1 Hz), 7.82 (qt, 1H, J = 4.7 Hz), 7.79 (s, 1H), 7.57 (d, 2H, J = 8.8 Hz), 7.45 (d, 2H, J = 8.8 Hz), 6.87 (d, 2H, J = 8.8 Hz), 4.57 (q, 2H, J = 5.8 Hz), 4.51 (t, 2H, J = 7.0 Hz), 2.61 (t, 2H, J = 7.0 Hz), 2.47 (d, 3H, J = 4.7 Hz), 1.26 (d, 6H, J = 5.8 Hz). LCMS: ret. time: 17.14 min.; purity: 99%; MS (*m/e*): 464 (MH⁺).

7.3.1059 N4-(3, 4-Ethylenedioxyphenyl)-5-fluoro-N2-[1-(2-methoxy-4-carbomethoxybenzyl)indazoline-6-yl]- 2,4-pyrimidinediamine (R935320)

In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N-(3, 4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine was reacted with 6-amino-1-(2-methoxy-3-carbomethoxybenzyl)indazoline to provide N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-[1-(2-methoxy-4-carbomethoxybenzyl)indazoline-6-yl]-2,4-pyrimidinediamine. ¹H NMR (DMSO-d₆): δ 9.36 (s, 1H), 9.18 (s, 1H), 8.08 (d, 1H, J = 3.5 Hz), 8.04 (s, 1H), 7.56 (d, 1H, J = 8.2 Hz), 7.45 (d, 1H, J = 1.8 Hz), 7.43-7.38 (m, 1H), 7.36-7.34 (m, 1H), 7.30 (dd, 1H, J = 1.7 and 8.8 Hz), 7.20 (dd, 1H, J = 2.3 and 8.8 Hz), 6.75 (d, 1H, J = 8.8 Hz), 6.68 (d, 1H, J = 8.2 Hz), 6.48 (dd, 1H, J = 1.7 and 8.2 Hz), 5.39 (s, 2H), 4.16 (s, 4H), 3.83 (s, 3H), 3.79 (s, 3H). LCMS: ret. time: 29.92 min.; purity: 80%; MS (*m/e*): 557 (MH⁺).

7.3.1060 5-Fluoro-N4-(3-hydroxyphenyl)-N2-[1-(2-methoxy-4-carbomethoxybenzyl)indazoline-6-yl]- 2,4-pyrimidinediamine (R935321)

In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N-(3-hydroxyphenyl)-4-pyrimidineamine was reacted with 6-amino-1-(2-methoxy-3-carbomethoxybenzyl)indazoline to provide 5-fluoro-N4-(3-hydroxyphenyl)-N2-[1-(2-methoxy-4-carbomethoxybenzyl)indazoline-6-yl]-2,4-pyrimidinediamine. ¹H NMR

(DMSO- d_6): δ 9.37 (s, 1H), 9.31(s, 1H), 9.23 (s, 1H), 8.11 (d, 1H, J = 3.5 Hz), 8.08 (s, 1H), 7.93 (s, 1H), 7.57 (d, 1H, J = 8.8 Hz), 7.45 (d, 1H, J = 1.7 Hz), 7.40 (dd, 1H, J = 1.7 and 8.8 Hz), 7.33-7.27 (, 2H), 7.13 (t, 1H, J = 1.7 Hz), 7.03 (t, 2H, J = 8.2 Hz), 6.67 (d, 1H, J = 8.2 Hz), 6.45 (dd, 1H, J = 1.7 and 8.2 Hz), 5.37 (s, 2H), 3.83 (s, 3H), 3.79 (s, 3H). LCMS: ret. time: 28.80 min.; purity: 92%; MS (m/e): 515 (MH^+).

7.3.1061 5-Fluoro-N4-(4-isopropoxyphenyl)-N2-[1-[2-methoxy-4-(*o*-toluylsulfonamidocarboxy)benzyl]indazoline-6-yl]-2,4-pyrimidinediamine (R935322)

In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N-(4-isopropoxyphenyl)-4-pyrimidineamine was reacted with 6-amino-1-[2-methoxy-4-(*o*-toluylsulfonamidocarboxy)benzyl]indazoline to provide 5-fluoro-N4-(4-isopropoxyphenyl)-N2-[1-[2-methoxy-4-(*o*-toluylsulfonamidocarboxy)benzyl]indazoline-6-yl]-2,4-pyrimidinediamine. 1H NMR (DMSO- d_6): δ 9.60 (s, 2H), 8.11 (d, 1H, J = 4.1 Hz), 8.00-7.92 (m, 3H), 7.61-7.53 (m, 4H), 7.47-7.24 (m, 5H), 6.81 (d, 2H, J = 8.8 Hz), 6.68 (d, 1H, J = 8.2 Hz), 5.34 (s, 2H), 4.48 (sept, 1H, J = 5.9 Hz), 3.82 (s, 3H), 2.55 (s, 3H), 1.21 (d, 6H, J = 5.9 Hz). LCMS: ret. time: 30.57 min.; purity: 95%; MS (m/e): 696 (MH^+).

7.3.1062 N4-(3, 4-Ethylenedioxyphenyl)-5-fluoro-N4-[1-[2-methoxy-4-(*o*-toluylsulfonamidocarboxy)benzyl]indazoline-6-yl]-2,4-pyrimidinediamine (R935323)

In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N-(3, 4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine was reacted with 6-amino-1-[2-methoxy-4-(*o*-toluylsulfonamidocarboxy)benzyl]indazoline to provide N4-(3, 4-Ethylenedioxyphenyl)-5-fluoro-N2-[1-[2-methoxy-4-(*o*-toluylsulfonamidocarboxy)benzyl]indazoline-6-yl]-2,4-pyrimidinediamine. 1H NMR (DMSO- d_6): δ 9.53 (s, 1H), 9.41 (s, 1H), 8.05 (d, 1H, J = 4.1 Hz), 7.96-7.90 (m, 3H), 7.55 (d, 1H, J = 8.8 Hz), 7.49 (dd, 1H, J = 7.6 Hz), 7.42-7.20 (m, 6H), 7.14-7.10 (m, 1H), 6.69 (d, 1H, J = 8.2 Hz), 6.60 (d, 1H, J = 8.8 Hz), 5.33 (s, 2H), 4.10 (s, 4H), 3.77 (s, 3H), 2.50 (s, 3H). LCMS: ret. time: 32.11 min.; purity: 93%; MS (m/e): 696 (MH^+).

7.3.1063 5-Fluoro-N4-(3-hydroxyphenyl)-N2-[1-[2-methoxy-4-(*o*-toluylsulfonamidocarboxy)benzyl]indazoline-6-yl]-2,4-pyrimidinediamine (R935324)

In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N-(3-hydroxyphenyl)-4-pyrimidineamine was reacted with 6-amino-1-[2-methoxy-4-(*o*-toluylsulfonamidocarboxy)benzyl]indazoline to provide 5-fluoro-N4-(3-hydroxyphenyl)-N2-[1-[2-methoxy-4-(*o*-toluylsulfonamidocarboxy)benzyl]indazoline-6-yl]-2,4-pyrimidinediamine. ¹H NMR (DMSO-d₆): δ 9.64 (s, 1H), 9.56 (s, 1H), 8.15 (d, 1H, J = 4.1 Hz), 8.00 (s, 1H), 7.97 (d, 2H, J = 8.8 Hz), 7.60 (d, 1H, J = 8.8 Hz), 7.53 (d, 1H, J = 1.2 and 8.8 Hz), 7.47-7.23 (m, 6H), 7.11 (t, 1H, J = 1.7 Hz), 7.03 (t, 1H, J = 8.2 Hz), 6.62 (d, 1H, J = 8.2 Hz), 6.48 (dd, 1H, J = 1.7 and 8.2 Hz), 5.36 (s, 2H), 3.82 (s, 3H), 2.55 (s, 3H). LCMS: ret. time: 29.79 min.; purity: 92%; MS (*m/e*): 654 (MH⁺).

7.3.1064 N4-(3, 4-Ethylenedioxyphenyl)-5-fluoro-N2-[2-(2-methoxy-4-carbomethoxybenzyl)indazoline-6-yl]- 2,4-pyrimidinediamine (R935336)

In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N-(3, 4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine was reacted with 6-amino-2-(2-methoxy-3-carbomethoxybenzyl)indazoline to provide N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-[2-(2-methoxy-4-carbomethoxybenzyl)indazoline-6-yl]-2,4-pyrimidinediamine. ¹H NMR (DMSO-d₆): δ 9.16 (s, 1H), 9.14 (s, 1H), 8.24 (s, 1H), 8.06 (s, 1H), 8.04 (d, 1H, J = 3.5 Hz), 7.51 (d, 2H, J = 7.7 Hz), 7.49 (s, 1H), 7.29-7.26 (m, 2H), 7.19 (d, 1H, J = 7.7 Hz), 6.92 (d, 1H, J = 8.8 Hz), 6.76 (d, 1H, J = 8.2 Hz), 5.58 (s, 2H), 4.22 (s, 4H), 3.92 (s, 3H), 3.82 (s, 3H). LCMS: ret. time: 10.91 min.; purity: 91%; MS (*m/e*): 557 (MH⁺).

7.3.1065 5-Fluoro-N4-(3-hydroxyphenyl)-N2-[2-(2-methoxy-4-carbomethoxybenzyl)indazoline-6-yl]- 2,4-pyrimidinediamine (R935337)

In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N-(3-hydroxyphenyl)-4-pyrimidineamine was reacted with 6-amino-2-(2-methoxy-3-carbomethoxybenzyl)indazoline to provide 5-fluoro-N4-(3-hydroxyphenyl)-N2-[2-(2-methoxy-4-carbomethoxybenzyl)indazoline-6-yl]-2,4-pyrimidinediamine. ¹H NMR

(DMSO- d_6): δ 9.31 (s, 1H), 9.17 (s, 1H), 9.15 (s, 1H), 8.26 (s, 1H), 8.09 (d, 1H, $J = 5.8$ Hz), 8.08 (s, 1H), 7.52 (app t, 3H, $J = 7.6$ Hz), 7.42 (d, 1H, $J = 8.2$ Hz), 7.23 (d, 1H, $J = 8.2$ Hz), 7.08 (app s, 1H), 7.03 (d, 1H, $J = 8.2$ Hz), 6.93 (d, 1H, $J = 7.6$ Hz), 6.43 (d, 1H, $J = 8.2$ Hz), 5.57 (s, 2H), 3.90 (s, 3H), 3.82 (s, 3H). LCMS: ret. time: 10.51 min.; purity: 93%; MS (m/e): 515 (MH^+).

7.3.1066 5-Fluoro-N4-(4-isopropoxyphenyl)-N2-[2-(2-methoxy-4-carbomethoxybenzyl)indazoline-6-yl]-2,4-pyrimidinediamine (R935338)

In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N-(4-isopropoxyphenyl)-4-pyrimidineamine was reacted with 6-amino-2-(2-methoxy-4-carbomethoxybenzyl)indazoline to provide 5-fluoro-N4-(4-isopropoxyphenyl)-N2-[2-(2-methoxy-4-carbomethoxybenzyl)indazoline-6-yl]-2,4-pyrimidinediamine. 1H NMR (DMSO- d_6): δ 9.20 (s, 1H), 9.16 (s, 1H), 8.26 (s, 1H), 8.16 (s, 1H), 8.06 (d, 1H, $J = 3.5$ Hz), 7.66 (d, 2H, $J = 8.8$ Hz), 7.52-7.48 (m, 3H), 7.15 (d, 1H, $J = 8.2$ Hz), 6.86 (d, 2H, $J = 8.8$ Hz), 6.81 (d, 1H, $J = 8.8$ Hz), 5.56 (s, 2H), 4.46 (sept, 1H, $J = 5.9$ Hz), 3.91 (s, 3H), 3.82 (s, 3H), 1.17 (d, 6H, $J = 5.9$ Hz). LCMS: ret. time: 11.94 min.; purity: 90%; MS (m/e): 557 (MH^+).

7.3.1067 N4-(3, 4-Ethylenedioxyphenyl)-5-fluoro-N2-[1-[2-methoxy-4-(*o*-toluylsulfonamidocarboxy)benzyl]indazoline-5-yl]-2,4-pyrimidinediamine (R935339)

In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N-(3, 4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine was reacted with 5-amino-1-[2-methoxy-4-(*o*-toluylsulfonamidocarboxy)benzyl]indazoline to provide N4-(3, 4-Ethylenedioxyphenyl)-5-fluoro-N2-[1-[2-methoxy-4-(*o*-toluylsulfonamidocarboxy)benzyl]indazoline-5-yl]-2,4-pyrimidinediamine. 1H NMR (DMSO- d_6): δ 9.57 (br s, 2H), 8.08 (d, 1H, $J = 3.5$ Hz), 8.01 (s, 1H), 7.99 (d, 1H, $J = 1.0$ Hz), 7.95 (s, 1H), 7.59-7.32 (m, 3H), 7.45-7.32 (m, 4H), 7.27-7.24 (m, 1H), 7.17-7.12 (m, 1H), 6.74 (d, 1H, $J = 8.7$ Hz), 6.65 (d, 1H, $J = 8.7$ Hz), 5.58 (s, 2H), 4.15 (s, 4H), 3.88 (s, 3H), 2.56 (s, 3H). LCMS: ret. time: 11.33 min.; purity: 98%; MS (m/e): 696 (MH^+).

7.3.1068 5-Fluoro-N4-(3-hydroxyphenyl)-N2-[1-[2-methoxy-4-(*o*-toluylsulfonamidocarboxy)benzyl]indazoline-5-yl]-2,4-pyrimidinediamine (R935340)

In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N-(3-hydroxyphenyl)-4-pyrimidineamine was reacted with 5-amino-1-[2-methoxy-4-(*o*-toluylsulfonamidocarboxy)benzyl]indazoline to provide 5-fluoro-N4-(3-hydroxyphenyl)-N2-[1-[2-methoxy-4-(*o*-toluylsulfonamidocarboxy)benzyl]indazoline-5-yl]-2,4-pyrimidinediamine. ¹H NMR (DMSO-*d*₆): δ 9.57 (s, 1H), 9.48 (s, 1H), 8.13 (app s, 2H), 8.00 (d, 1H, J = 8.2 Hz), 7.94 (s, 1H), 7.59-7.32 (m, 7H), 7.18 (d, 1H, J = 8.2 Hz), 7.06 (app t, 3H, J = 8.8 Hz), 6.64 (d, 1H, J = 8.2 Hz), 6.55 (d, 1H, J = 8.2 Hz), 5.57 (s, 2H), 3.88 (s, 3H), 2.56 (s, 3H). LCMS: ret. time: 10.16 min.; purity: 97%; MS (*m/e*): 654 (MH⁺).

7.3.1069 N4-(4-Chlorophenyl)-5-fluoro-N2-(1-methyl-indazoline-5-yl)-2,4-pyrimidinediamine (R935351)

In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N-(4-chlorophenyl)-5-fluoro 4-pyrimidineamine and 1-methyl-5-aminoindazoline were reacted to give N4-(4-chlorophenyl)-5-fluoro-N2-(1-methyl-indazoline-5-yl)-2,4-pyrimidinediamine. ¹H NMR (DMSO-*d*₆): δ 9.86 (s, 1H), 9.61 (s, 1H), 8.17 (d, 1H, J = 4.1 Hz), 8.00 (s, 1H), 7.88 (s, 1H), 7.78 (d, 2H, J = 8.8 Hz), 7.57 (d, 1H, J = 8.8 Hz), 7.43 (d, 1H, J = 8.8 Hz), 7.34 (d, 2H, J = 8.8 Hz), 4.00 (s, 3H). LCMS: ret. time: 10.64 min.; purity: 94%; MS (*m/e*): 369 (MH⁺).

7.3.1070 N4-(4-Chlorophenyl)-5-fluoro-N2-(indazoline-6-yl)-2,4-pyrimidinediamine (R935352)

In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N-(4-chlorophenyl)-5-fluoro 4-pyrimidineamine and 6-aminoindazoline were reacted to give N4-(4-chlorophenyl)-5-fluoro-N2-(indazoline-6-yl)-2,4-pyrimidinediamine. ¹H NMR (DMSO-*d*₆): δ 10.18 (s, 1H), 10.02 (s, 1H), 8.26 (d, 1H, J = 4.1 Hz), 7.98 (s, 1H), 7.84 (d, 1H, J = 8.8 Hz), 7.82 (d, 2H, J = 8.8 Hz), 7.65 (d, 1H, J = 8.8 Hz), 7.35 (d, 2H, J = 8.8 Hz), 7.19 (d, 1H, J = 8.8 Hz). LCMS: ret. time: 10.80 min.; purity: 90%; MS (*m/e*): 355 (MH⁺).

7.3.1071 N4-(4-Chlorophenyl)-N2-[1-(2-ethoxycarbonylethyl)indazoline-5-yl]-5-fluoro-2,4-pyrimidinediamine (R935353)

In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N-(4-chlorophenyl)-5-fluoro-4-pyrimidineamine was reacted with 5-amino-1-(2-ethoxycarbonylethyl)indazoline to provide N4-(4-chlorophenyl)-N2-[1-(2-ethoxycarbonylethyl)indazoline-5-yl]-5-fluoro-2,4-pyrimidinediamine. ¹H NMR (DMSO-d₆): δ 10.37 (s, 1H), 10.17 (s, 1H), 8.26 (d, 1H, J = 5.3 Hz), 7.96 (s, 1H), 7.88 (s, 1H), 7.33-7.66 (m, 3H), 7.40 (d, 1H, J = 8.8 Hz), 7.35 (d, 2H, J = 8.8 Hz), 4.61 (t, 2H, J = 6.4 Hz), 3.97 (qt, 2H, J = 7.0 Hz), 2.91 (t, 2H, J = 6.4 Hz), 1.05 (t, 3H, J = 7.0 Hz). LCMS: ret. time: 11.85 min.; purity: 95%; MS (*m/e*): 455 (MH⁺).

7.3.1072 N4-(3-Chloro-4-trifluoromethoxy-phenyl)-N2-[1-(2-ethoxycarbonylethyl)indazoline-5-yl]-5-fluoro-2,4-pyrimidinediamine (R935354)

In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N-(3-chloro-trifluoromethoxy-phenyl)-5-fluoro-4-pyrimidineamine was reacted with 5-amino-1-(2-ethoxycarbonylethyl)indazoline to provide N4-(3-chloro-4-trifluoromethoxy-phenyl)-N2-[1-(2-ethoxycarbonylethyl)indazoline-5-yl]-5-fluoro-2,4-pyrimidinediamine. ¹H NMR (DMSO-d₆): δ 9.63 (s, 1H), 9.30 (s, 1H), 8.17 (d, 1H, J = 3.5 Hz), 8.10 (t, 1H, J = 2.3 Hz), 8.01 (s, 1H), 7.87 (s, 1H), 7.86 (d, 1H, J = 8.2 Hz), 7.57 (d, 1H, J = 9.4 Hz), 7.47 (t, 2H, J = 10.0 Hz), 4.56 (t, 2H, J = 6.9 Hz), 3.97 (qt, 2H, J = 7.0 Hz), 2.88 (t, 2H, J = 6.9 Hz), 1.06 (t, 3H, J = 7.0 Hz). LCMS: ret. time: 14.4 min.; purity: 95%; MS (*m/e*): 539 (MH⁺).

7.3.1073 N4-(3, 4-Dichlorophenyl)-5-fluoro-N2-(1-methylindazoline-5-yl)-2,4-pyrimidinediamine (R935355)

In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N-(3, 4-dichlorophenyl)-5-fluoro 4-pyrimidineamine and 1-methyl-5-aminoindazoline were reacted to give N4-(3, 4-dichlorophenyl)-5-fluoro-N2-(1-methylindazoline-5-yl)-2,4-pyrimidinediamine. ¹H NMR (DMSO-d₆): δ 9.63 (s, 1H), 9.35 (s, 1H), 8.17 (d, 1H, J = 3.5 Hz), 8.08 (s, 1H), 8.01 (s, 1H), 7.86 (s, 1H), 7.79 (d, 1H, J = 8.8 Hz), 7.53 (d, 2H, J = 8.2 Hz), 7.47 (d, 1H, J = 8.2 Hz), 3.99 (s, 3H). LCMS: ret. time: 12.30 min.; purity: 98%; MS (*m/e*): 404 (MH⁺).

7.3.1074 5-Fluoro-N2-(1-methylindazoline-5-yl)-N4-(3-trifluoromethoxyphenyl)-2,4-pyrimidinediamine (R935356)

In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N-(3-trifluoromethoxyphenyl)-4-pyrimidineamime and 1-methyl-5-aminoindazoline were reacted to give 5-fluoro-N2-(1-methylindazoline-5-yl)-N4-(3-trifluoromethoxyphenyl)-2,4-pyrimidinediamine. ¹H NMR (DMSO-d₆): δ 10.37 (s, 1H), 10.17 (s, 1H), 8.25 (d, 1H, J = 4.1 Hz), 7.92 (s, 2H), 7.84 (d, 1H, J = 9.4 Hz), 7.75 (s, 1H), 7.59 (d, 1H, J = 8.8 Hz), 7.45 (d, 1H, J = 9.4 Hz), 7.38 (d, 1H, J = 9.4 Hz), 7.08 (d, 1H, J = 8.8 Hz), 3.99 (s, 3H). LCMS: ret. time: 12.13 min.; purity: 94%; MS (*m/e*): 419 (MH⁺).

7.3.1075 N4-(3, 4-Difluoromethylendioxyphenyl)-5-fluoro-N2-(1-methylindazoline-5-yl)-2,4-pyrimidinediamine (R935357)

In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N-(3, 4-difluoromethylendioxyphenyl)-5-fluoro-4-pyrimidineamime and 1-methyl-5-aminoindazoline were reacted to give N4-(3, 4-difluoromethylendioxyphenyl)-5-fluoro-N2-(1-methylindazoline-5-yl)-2,4-pyrimidinediamine. ¹H NMR (DMSO-d₆): δ 9.84 (s, 1H), 9.54 (s, 1H), 8.16 (d, 1H, J = 4.1 Hz), 8.00 (s, 2H), 7.87 (s, 1H), 7.55-7.32 (m, 4H), 3.99 (s, 3H). LCMS: ret. time: 11.26 min.; purity: 96%; MS (*m/e*): 415 (MH⁺).

7.3.1076 N4-(3, 4-Difluorophenyl)-5-fluoro-N2-(1-methylindazoline-5-yl)-2,4-pyrimidinediamine (R935358)

In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N-(3, 4-difluorophenyl)-5-fluoro-4-pyrimidineamime and 1-methyl-5-aminoindazoline were reacted to give N4-(3, 4-difluorophenyl)-5-fluoro-N2-(1-methylindazoline-5-yl)-2,4-pyrimidinediamine. ¹H NMR (DMSO-d₆): δ 9.50 (s, 1H), 9.27 (s, 1H), 8.13 (d, 1H, J = 4.1 Hz), 8.08 (app s, 2H), 7.85 (s, 1H), 7.50 (app s, 3H), 7.37 (q, 1H, J = 9.4 Hz), 3.99 (s, 3H). LCMS: ret. time: 10.42 min.; purity: 90%; MS (*m/e*): 371 (MH⁺).

7.3.1077 N4-(3-chloro-4-trifluoromethoxyphenyl)-5-fluoro-N2-(1-methylindazoline-5-yl)-2,4-pyrimidinediamine (R935359)

In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N-(3-chloro-4-trifluoromethoxyphenyl)-

5-fluoro-4-pyrimidineamine and 1-methyl-5-aminoindazoline were reacted to give N4-(3-chloro-4-trifluoromethoxyphenyl)-5-fluoro-N2-(1-methylindazoline-5-yl)-2,4-pyrimidinediamine. ¹H NMR (DMSO-d₆): δ 9.79 (s, 1H), 9.45 (s, 1H), 8.19 (d, 1H, J = 4.1 Hz), 8.09 (t, 1H, J = 2.8 Hz), 8.00 (s, 1H), 7.85-7.81 (m, 2H), 7.51 (d, 1H, J = 8.8 Hz), 7.48-7.44 (m, 2H), 3.99 (s, 3H). LCMS: ret. time: 13.14 min.; purity: 92%; MS (*m/e*): 453 (MH⁺).

7.3.1078 N2-[1-(2-Ethoxycarbonyl)ethyl]indazoline-5-yl]-5-fluoro-N4-(3-trifluoromethoxyphenyl)-2,4-pyrimidinediamine (R935360)

In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N-(3-trifluoromethoxyphenyl)-4-pyrimidineamine was reacted with 5-amino-1-(2-ethoxycarbonyl)indazoline to provide N2-[1-(2-ethoxycarbonyl)ethyl]indazoline-5-yl]-5-fluoro-N4-(3-trifluoromethoxyphenyl)-2,4-pyrimidinediamine. ¹H NMR (DMSO-d₆): δ 9.55 (s, 1H), 9.26 (s, 1H), 8.15 (d, 1H, J = 3.5 Hz), 8.05 (s, 1H), 7.95 (d, 1H, J = 8.2 Hz), 7.88 (s, 1H), 7.78 (s, 1H), 7.58 (dd, 1H, J = 8.8 and 7.4 Hz), 7.39 (t, 1H, J = 8.2 Hz), 7.01 (d, 1H, J = 8.8 Hz), 4.56 (t, 2H, J = 7.0 Hz), 3.97 (q, 4H, J = 7.0 Hz), 2.88 (t, 2H, J = 7.0 Hz), 1.06 (t, 3H, J = 7.0 Hz). LCMS: ret. time: 13.22 min.; purity: 95%; MS (*m/e*): 505 (MH⁺).

7.3.1079 5-Fluoro-N2-[1-[2(*N*-methylaminocarbonyl)ethyl]indazoline-5-yl]-N4-(3-trifluoromethoxyphenyl)-2,4-pyrimidinediamine (R935361)

In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(*N*-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, N2-[1-(2-ethoxycarbonyl)ethyl]indazoline-5-yl]-5-fluoro-N4-(3-trifluoromethoxyphenyl)-2,4-pyrimidinediamine and Me₂NH.HCl were reacted to provide 5-fluoro-N2-[1-[2(*N*-methylaminocarbonyl)ethyl]indazoline-5-yl]-N4-(3-trifluoromethoxyphenyl)-2,4-pyrimidinediamine. ¹H NMR (DMSO-d₆): δ 9.55 (s, 1H), 9.25 (s, 1H), 8.15 (d, 1H, J = 3.5 Hz), 8.04 (s, 1H), 7.96 (d, 1H, J = 8.2 Hz), 7.87 (s, 1H), 7.83 (qt, 1H, J = 4.9 Hz), 7.70 (s, 1H), 7.49 (dd, 2H, J = 8.2 and 9.4 Hz), 7.40 (d, 1H, J = 8.8 Hz), 7.01 (d, 1H, J = 8.8 Hz), 4.52 (t, 2H, J = 7.0 Hz), 2.63 (t, 2H, J = 7.0 Hz), 2.49 (d, 3H, J = 4.7 Hz). LCMS: ret. time: 10.00 min.; purity: 100%; MS (*m/e*): 490 (MH⁺).

7.3.1080 5-Fluoro-N2-[1-(3-hydroxypropyl)indazoline-5-yl]-N4-(3-trifluoromethoxyphenyl)-2,4-pyrimidinediamine (R935362)

In like manner to the preparation of N2-(3, 4-ethylenedioxyphenyl)-5-fluoro-N4-[4(2-hydroxy-1,1-dimethylethyl)phenyl]-2,4-pyrimidinediamine, N2-[1-(2-ethoxycarbonylethyl)indazoline-5-yl]- 5-fluoro-N4-(3-trifluoromethoxyphenyl)-2,4-pyrimidinediamine was reacted with DIBAL-H to produce 5-fluoro-N2-[1-(3-hydroxypropyl)indazoline-5-yl]-N4-(3-trifluoromethoxyphenyl)-2,4-pyrimidinediamine. ¹H NMR (DMSO-d₆): δ 9.55 (s, 1H), 9.24 (s, 1H), 8.15 (d, 1H, J = 2.9 Hz), 8.05 (s, 1H), 7.92 (d, 1H, J = 7.6 Hz), 7.87 (s, 1H), 7.78 (s, 1H), 7.50 (s, 2H), 7.39 (t, 1H, J = 8.2 Hz), 7.01 (d, 1H, J = 7.6 Hz), 4.56 (t, 1H, J = 5.2 Hz), 4.38 (t, 2H, J = 7.0 Hz), 3.35 (dd, 2H, J = 5.2 and 7.0 Hz), 1.84 (qt, 2H, J = 7.0 Hz). LCMS: ret. time: 10.42 min.; purity: 97%; MS (*m/e*): 463 (MH⁺).

7.3.1081 5-Fluoro-N2-(indazoline-6-yl)-N4-(3-trifluoromethoxyphenyl)-2,4-pyrimidinediamine (R935363)

In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N-(3-trifluoromethoxyphenyl)-4-pyrimidineamine and 6-aminoindazoline were reacted to give 5-fluoro-N2-(indazoline-6-yl)-N4-(3-trifluoromethoxyphenyl)-2,4-pyrimidinediamine. ¹H NMR (DMSO-d₆): δ 12.72(s, 1H), 9.60 (s, 1H), 9.42 (s, 1H), 8.21 (d, 1H, J = 3.5 Hz), 8.06 (br s, 2H), 7.89 (s, 1H), 7.83 (s, 1H), 7.57 (d, 1H, J = 8.8 Hz), 7.42 (t, 1H, J = 8.2 Hz), 7.27 (d, 1H, J = 8.8 Hz), 7.00 (d, 1H, J = 8.2 Hz). LCMS: ret. time: 12.17 min.; purity: 97%; MS (*m/e*): 405 (MH⁺).

7.3.1082 5-Fluoro-N2-(indazoline-5-yl)-N4-(3-trifluoromethoxyphenyl)-2,4-pyrimidinediamine (R935364)

In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N-(3-trifluoromethoxyphenyl)-4-pyrimidineamine and 5-aminoindazoline were reacted to give 5-fluoro-N2-(indazoline-5-yl)-N4-(3-trifluoromethoxyphenyl)-2,4-pyrimidinediamine. ¹H NMR (DMSO-d₆): δ 12.85 (s, 1H), 9.54 (s, 1H), 9.23 (s, 1H), 8.15 (d, 1H, J = 3.5 Hz), 8.05 (s, 1H), 7.93 (d, 1H, J = 8.2 Hz), 7.89 (s, 1H), 7.78 (s, 1H), 7.48-7.35 (m, 3H), 7.01 (d, 1H, J = 8.2 Hz). LCMS: ret. time: 10.44 min.; purity: 98%; MS (*m/e*): 405 (MH⁺).

7.3.1083 N4-(4-Chlorophenyl)-5-fluoro-N2-(indazoline-5-yl)-2,4-pyrimidinediamine (R935365)

In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N-(4-chlorophenyl)-5-fluoro 4-pyrimidineamime and 5-aminoindazoline were reacted to give N4-(4-chlorophenyl)-5-fluoro-N2-(indazoline-5-yl)-2,4-pyrimidinediamine. ¹H NMR (DMSO-d₆): δ 12.85 (s, 1H), 9.43 (s, 1H), 9.19 (s, 1H), 8.11 (d, 1H, J = 3.5 Hz), 8.08 (s, 1H), 7.87 (s, 1H), 7.82 (dd, 2H, J = 3.0 and 8.8 Hz), 7.42 (dd, 2H, J = 3.0 and 8.8 Hz), 7.31 (d, 2H, J = 8.8 Hz). LCMS: ret. time: 9.07 min.; purity: 91%; MS (*m/e*): 355 (MH⁺).

7.3.1084 N4-(3-Chloro-4-trifluoromethoxyphenyl)-5-fluoro-N2-(indazoline-5-yl)-2,4-pyrimidinediamine (R935366)

In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N-(3-chloro-4-trifluoromethoxyphenyl)-5-fluoro-4-pyrimidineamime and 5-aminoindazoline were reacted to give N4-(3-chloro-4-trifluoromethoxyphenyl)-5-fluoro-N2-(indazoline-5-yl)-2,4-pyrimidinediamine. ¹H NMR (DMSO-d₆): δ 12.90 (s, 1H), 9.45 (s, 1H), 9.27 (s, 1H), 8.15 (d, 1H, J = 3.5 Hz), 8.11 (t, 1H, J = 3.0 Hz), 8.02 (s, 1H), 7.87 (s, 1H), 7.84 (d, 1H, J = 8.8 Hz), 7.47 (d, 2H, J = 8.8 Hz), 7.44 (d, 1H, J = 8.8 Hz). LCMS: ret. time: 11.65 min.; purity: 98%; MS (*m/e*): 439 (MH⁺).

7.3.1085 5-Fluoro-N4-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-N2-(3, 4,5-trimethoxyphenyl)-2,4-pyrimidinediamine (R935367)

In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-4-pyrimidineamine and 3, 4,5-trimethoxyaniline were reacted by microwave heating at 180 °C. Upon concentration of the ethanol and addition of 2N HCl provided 5-fluoro-N4-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-N2-(3, 4,5-trimethoxyphenyl)-2,4-pyrimidinediamine as fine flakes of the solid. ¹H NMR (DMSO-d₆): δ 9.59 (s, 1H), 9.25 (s, 1H), 8.09 (d, 1H, J = 3.5 Hz), 8.01 (dd, 2H, J = 5.3 and 1.2 Hz), 7.39 (dd, 2H, J = 3.1 and 8.8 Hz), 7.60-7.54 (m, 3H), 7.03 (d, 2H, J = 8.8 Hz), 6.94 (d, 2H, J = 3.1 Hz), 5.57 (s, 2H), 3.59 (s, 6H), 3.57 (s, 3H). LCMS: ret. time: 13.00 min.; purity: 97%; MS (*m/e*): 547 (MH⁺).

7.3.1086 N4-(3-Chloro-4-trifluoromethoxyphenyl)-5-fluoro-N2-(indazoline-6-yl)-2,4-pyrimidinediamine (R935368)

In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N-(3-chloro-4-trifluoromethoxyphenyl)-5-fluoro-4-pyrimidineamime and 6-aminoindazoline were reacted to give N4-(3-chloro-4-trifluoromethoxyphenyl)-5-fluoro-N2-(indazoline-6-yl)-2,4-pyrimidinediamine. ¹H NMR (DMSO-d₆): δ 12.73 (s, 1H), 9.67 (s, 1H), 9.46 (s, 1H), 8.21 (d, 1H, J = 3.5 Hz), 8.17 (app d, 1H, J = 8.8 Hz), 8.04 (br s, 1H), 7.97 (dt, 1H, J = 2.4 and 9.3 Hz), 7.89 (s, 1H), 7.58 (d, 1H, J = 8.8 Hz), 7.47 (d, 1H, J = 9.3 Hz), 7.27 (dd, 1H, J = 1.7 and 8.8 Hz). LCMS: ret. time: 13.08 min.; purity: 96%; MS (*m/e*): 439 (MH⁺).

7.3.1087 N4-(3-Chloro-4-trifluoromethoxyphenyl)-5-fluoro-N2-[1-[2(*N*-methylaminocarbonyl)ethyl]indazoline-5-yl]-2,4-pyrimidinediamine (R935369)

In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(*N*-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, N4-(3-chloro-4-trifluoromethoxyphenyl)-N2-[1-(2-ethoxycarbonyl)ethyl]indazoline-5-yl]-5-fluoro-2,4-pyrimidinediamine and Me₂NH.HCl were reacted to provide N4-(3-Chloro-4-trifluoromethoxyphenyl)-5-fluoro-N2-[1-[2(*N*-methylaminocarbonyl)ethyl]indazoline-5-yl]-2,4-pyrimidinediamine. ¹H NMR (DMSO-d₆): δ 9.62 (s, 1H), 9.29 (s, 1H), 8.17 (d, 1H, J = 3.5 Hz), 8.11 (t, 1H, J = 2.4 Hz), 8.02 (app s, 1H), 7.88-7.82 (m, 3H), 7.53 (d, 1H, J = 9.3 Hz), 7.47 (d, 2H, J = 8.8 Hz), 4.52 (t, 2H, J = 7.0 Hz), 2.48 (t, 2H, J = 7.0 Hz), 2.48 (d, 3H, J = 4.7 Hz). LCMS: ret. time: 10.51 min.; purity: 99%; MS (*m/e*): 524 (MH⁺).

7.3.1088 N4-(3-Chloro-4-trifluoromethoxyphenyl)-5-fluoro-N2-[1-(3-hydroxypropyl)indazoline-5-yl]-2,4-pyrimidinediamine (R935370)

In like manner to the preparation of N2-(3, 4-ethylenedioxyphenyl)-5-fluoro-N4-[4(2-hydroxy-1,1-dimethylethyl)phenyl]-2,4-pyrimidinediamine, N4-(3-chloro-4-trifluoromethoxyphenyl)-N2-[1-(2-ethoxycarbonyl)ethyl]indazoline-5-yl]-5-fluoro-2,4-pyrimidinediamine was reacted with DIBAL-H to produce N4-(3-chloro-4-trifluoromethoxyphenyl)-5-fluoro-N2-[1-(3-hydroxypropyl)indazoline-5-yl]-2,4-pyrimidinediamine. ¹H NMR (DMSO-d₆): δ 9.62 (s, 1H), 9.28 (s, 1H), 8.17 (d, 1H, J = 3.5 Hz), 8.11 (s, 1H), 8.02 (s, 1H), 7.85 (s, 2H), 7.53 (t, 2H, J = 8.8 Hz), 7.46 (t, 1H, J = 8.8

Hz), 4.56 (t, 1H, J = 5.8 Hz), 4.38 (t, 2H, J = 6.4 Hz), 3.35 (dd, 2H, J = 5.8 and 6.4 Hz), 1.93 (q, 2H, J = 6.4 Hz). LCMS: ret. time: 11.33 min.; purity: 99%; MS (*m/e*): 497 (MH⁺).

7.3.1089 N4-(3, 4-Dichlorophenyl)-5-fluoro-N2-(indazoline-5-yl)-2,4-pyrimidinediamine (R935371)

5 In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N-(3, 4-dichlorophenyl)-5-fluoro 4-pyrimidineamine and 5-aminoindazoline were reacted to give N4-(3, 4-dichlorophenyl)-5-fluoro-N2-(indazoline-5-yl)-2,4-pyrimidinediamine. ¹H NMR (DMSO-d₆): δ 9.90 (s, 1H), 9.60 (s, 1H), 8.20 (d, 1H, J = 4.2 Hz), 8.06 (t, 1H, J = 2.3 Hz), 7.92 (s, 2H), 7.73 (d, 1H, J = 8.8 Hz), 7.51-7.40 (m, 3H). LCMS: ret. time: 9.83 min.; purity: 98%; MS (*m/e*): 390 (MH⁺).

7.3.1090 N4-(3, 4-Dichlorophenyl)-5-fluoro-N2-(indazoline-6-yl)-2,4-pyrimidinediamine (R935372)

15 In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N-(3, 4-dichlorophenyl)-5-fluoro 4-pyrimidineamine and 6-aminoindazoline were reacted to give N4-(3, 4-dichlorophenyl)-5-fluoro-N2-(indazoline-6-yl)-2,4-pyrimidinediamine. ¹H NMR (DMSO-d₆): δ 12.82 (s, 1H), 9.63 (s, 1H), 9.48 (s, 1H), 8.22 (d, 1H, J = 4.3 Hz), 8.15 (t, 1H, J = 2.3 Hz), 8.02 (s, 1H), 7.92-7.90 (m, 2H), 7.59 (d, 1H, J = 8.8 Hz), 7.52 (d, 1H, J = 8.8 Hz), 7.26 (dd, 1H, J = 1.7 and 8.8 Hz). LCMS: ret. time: 11.73 min.; purity: 99%; MS (*m/e*): 390 (MH⁺).

7.3.1091 N4-(3, 4-Difluoromethylendioxyphenyl)-5-fluoro-N2-(indazoline-5-yl)-2,4-pyrimidinediamine (R935373)

25 In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N-(3, 4-difluoromethylendioxyphenyl)-5-fluoro-4-pyrimidineamine and 5-aminoindazoline were reacted to give N4-(3, 4-difluoromethylendioxyphenyl)-5-fluoro-N2-(indazoline-5-yl)-2,4-pyrimidinediamine. ¹H NMR (DMSO-d₆): δ 10.40 (s, 1H), 10.11 (s, 1H), 8.25 (d, 1H, J = 4.5 Hz), 7.95 (s, 1H), 7.89 (app s, 2H), 7.49 (d, 1H, J = 8.8 Hz), 7.37 (app d, 3H, J = 8.2 Hz). LCMS: ret. time: 8.56 min.; purity: 99%; MS (*m/e*): 401 (MH⁺).

7.3.1092 N4-(3, 4-Difluoromethylenedioxyphenyl)-5-fluoro-N2-(indazoline-6-yl)-2,4-pyrimidinediamine (R935374)

In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N-(3, 4-difluoromethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine and 6-aminoindazoline were reacted to give N4-(3, 4-difluoromethylenedioxyphenyl)-5-fluoro-N2-(indazoline-6-yl)-2,4-pyrimidinediamine. ¹H NMR (DMSO-d₆): δ 9.53 (s, 1H), 9.52 (s, 1H), 8.21 (d, 1H, J = 4.5 Hz), 8.10 (s, 1H), 8.01 (s, 1H), 7.92 (s, 1H), 7.59 (d, 1H, J = 8.8 Hz), 7.48 (dt, 1H, J = 2.3 and 8.8 Hz), 7.34 (d, 1H, J = 8.2 Hz), 7.21 (dd, 1H, J = 2.3 and 8.8 Hz). LCMS: ret. time: 11.29 min.; purity: 90%; MS (*m/e*): 401 (MH⁺).

7.3.1093 N4-(6-Chloro-3-pyridyl)-5-fluoro-N2-(1-methylindazoline-5-yl)-2,4-pyrimidinediamine (R935375)

In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N-(6-chloro-3-pyridyl)-5-fluoro-4-pyrimidineamine and 5-amino-1-methylindazoline were reacted to give N4-(6-chloro-3-pyridyl)-5-fluoro-N2-(1-methylindazoline-5-yl)-2,4-pyrimidinediamine. ¹H NMR (DMSO-d₆): δ 9.96 (s, 1H), 9.58 (s, 1H), 8.86 (s, 1H), 8.25 (dt, 1H, J = 3.9 and 8.8 Hz), 8.20 (d, 1H, J = 4.1 Hz), 8.04 (s, 1H), 7.55 (d, 1H, J = 8.8 Hz), 7.44 (d, 2H, J = 8.8 Hz), 4.00 (s, 3H). LCMS: ret. time: 8.95 min.; purity: 100%; MS (*m/e*): 370 (MH⁺).

7.3.1094 N4-(6-Chloro-3-pyridyl)-5-fluoro-N2-(indazoline-5-yl)-2,4-pyrimidinediamine (R935376)

In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N-(6-chloro-3-pyridyl)-5-fluoro-4-pyrimidineamine and 5-aminoindazoline were reacted to give N4-(6-chloro-3-pyridyl)-5-fluoro-N2-(indazoline-5-yl)-2,4-pyrimidinediamine. ¹H NMR (DMSO-d₆): δ 9.78 (s, 1H), 9.41 (s, 1H), 8.88 (s, 1H), 8.24 (d, 1H, J = 8.2 Hz), 8.18 (d, 1H, J = 3.5 Hz), 8.06 (s, 1H), 7.92 (s, 1H), 7.42 (app s, 3H). LCMS: ret. time: 7.87 min.; purity: 90%; MS (*m/e*): 356 (MH⁺).

7.3.1095 N4-(6-Chloro-3-pyridyl)-N2-[1-(2-ethoxycarbonylethyl)indazoline-5-yl]-5-fluoro-2,4-pyrimidinediamine (R935377)

In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N-(6-chloro-3-pyridyl)-5-fluoro-4-pyrimidineamine and 5-amino-1-(2-ethoxycarbonylethyl)indazoline were reacted to give N4-(6-chloro-3-pyridyl)-N2-[1-(2-ethoxycarbonylethyl)indazoline-5-yl]-5-fluoro-2,4-pyrimidinediamine. ¹H NMR (DMSO-d₆): δ 10.37 (s, 1H), 10.04 (s, 1H), 8.78 (s, 1H), 8.28 (d, 1H, J = 4.8 Hz), 8.20 (dt, 1H, J = 2.8 and 8.8 Hz), 7.96 (s, 1H), 7.92 (s, 1H), 7.65 (d, 1H, J = 8.8 Hz), 7.45 (d, 1H, J = 8.8 Hz), 7.41 (d, 1H, J = 8.8 Hz), 4.59 (t, 2H, J = 6.0 Hz), 3.97 (qt, 2H, J = 7.0 Hz), 2.90 (t, 2H, J = 6.4 Hz), 1.06 (t, 3H, J = 7.0 Hz). LCMS: ret. time: 10.87 min.; purity: 94%; MS (m/e): 456 (MH⁺).

7.3.1096 N4-(6-Chloro-3-pyridyl)-5-fluoro-N2-[1-[2(N-methylaminocarbonyl)ethyl]indazoline-5-yl]-2,4-pyrimidinediamine (R935378)

In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, N4-(6-chloro-3-pyridyl)-N2-[1-(2-ethoxycarbonylethyl)indazoline-5-yl]-5-fluoro-2,4-pyrimidinediamine and Me₂NH.HCl were reacted to provide N4-(6-Chloro-3-pyridyl)-5-fluoro-N2-[1-[2(N-methylaminocarbonyl)ethyl]indazoline-5-yl]-2,4-pyrimidinediamine. ¹H NMR (DMSO-d₆): δ 9.67 (s, 1H), 9.31 (s, 1H), 8.88 (s, 1H), 8.27 (dt, 1H, J = 3.0 and 8.8 Hz), 8.17 (d, 1H, J = 3.5 Hz), 8.08 (s, 1H), 7.88 (s, 1H), 7.83 (q, 1H, J = 5.3 Hz), 7.53 (d, 1H, J = 8.8 Hz), 7.45 (d, 1H, J = 8.8 Hz), 4.53 (t, 2H, J = 7.0 Hz), 2.63 (t, 2H, J = 7.0 Hz), 2.49 (d, 3H, J = 5.3 Hz). LCMS: ret. time: 7.62 min.; purity: 89%; MS (m/e): 441 (MH⁺).

7.3.1097 N4-(6-Chloro-3-pyridyl)-5-fluoro-N2-[1-(3-hydroxypropyl)indazoline-5-yl]-2,4-pyrimidinediamine (R935379)

In like manner to the preparation of N2-(3, 4-ethylenedioxyphenyl)-5-fluoro-N4-[4(2-hydroxy-1,1-dimethylethyl)phenyl]-2,4-pyrimidinediamine, N4-(6-chloro-3-pyridyl)-N2-[1-(2-ethoxycarbonylethyl)indazoline-5-yl]-5-fluoro-2,4-pyrimidinediamine was reacted with DIBAL-H to produce N4-(6-chloro-3-pyridyl)-5-fluoro-N2-[1-(3-hydroxypropyl)indazoline-5-yl]-2,4-pyrimidinediamine. ¹H NMR (DMSO-d₆): LCMS: ret. time: 8.02 min.; purity: 98%; MS (m/e): 414 (MH⁺).

7.3.1098 N4-(2,6-Dimethoxy-3-pyridyl)-5-fluoro-N2-[1-methylindazoline-5-yl]-2,4-pyrimidinediamine (R935380)

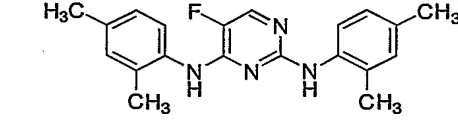
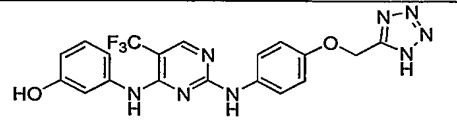
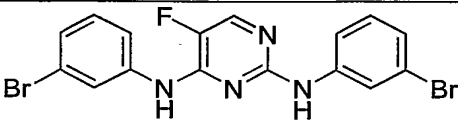
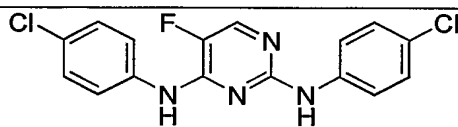
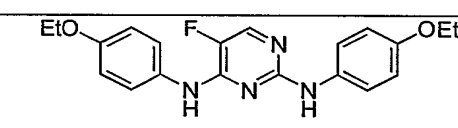
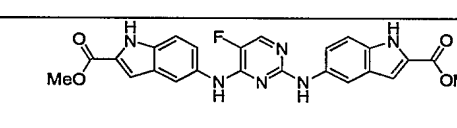
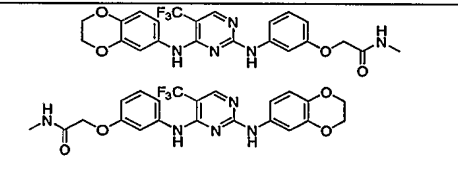
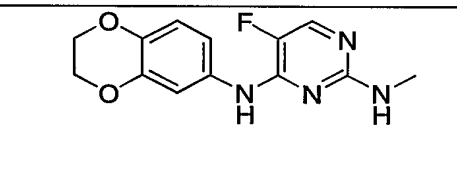
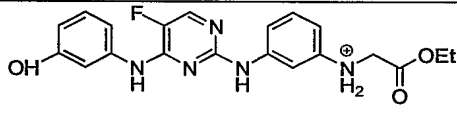
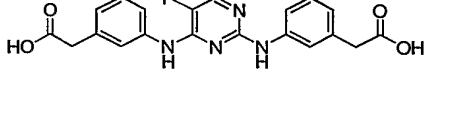
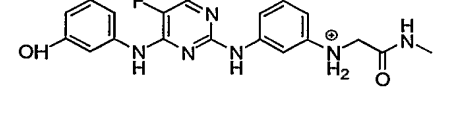
In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N-(2,6-dimethoxy-3-pyridyl)-6-5-fluoro-4-pyrimidineamine and 1-methyl-5-aminoindazoline were reacted to give N4-(2,6-dimethoxy-3-pyridyl)-5-fluoro-N2-[1-methylindazoline-5-yl]-2,4-pyrimidinediamine. ¹H NMR (DMSO-d₆): δ 9.08 (s, 1H), 8.68 (s, 1H), 8.01 (d, 1H, J = 4.1 Hz), 7.96 (s, 1H), 7.76 (dd, 1H, J = 4.1 and 8.8 Hz), 7.65 (s, 1H), 7.37 (d, 1H, J = 8.8 Hz), 7.34 (d, 1H, J = 8.2 Hz), 6.46 (d, 1H, J = 8.2 Hz), 3.94 (s, 3H), 3.91 (s, 3H), 3.83 (s, 3H). LCMS: ret. time: 9.57 min.; purity: 92%; MS (m/e): 396 (MH⁺).

7.3.1099 Additional 2,4-Pyrimidinediamine

Compounds R008951, R008952, R008953, R008955, R008956, R008958, R070153 and R070790 (structures provided below) were purchased from Contact Services.

Additional compounds whose structures are provided below were synthesized using methods similar to those described in the previous examples.

| | | | |
|-------------------------------|--|--------------------|--|
| R008951 R067962 R926209 | | R088814 R926017 | |
| R008952 R067963 | | R088815 | |
| R008953 R067964 | | R091880 | |
| R008955 R081166 | | R092788 | |

| | | | |
|--------------------|---|---------|--|
| R008956 R070791 |  | R920846 |  |
| R008958 |  | | |
| R070153 |  | | |
| R070790 R926036 |  | R926593 |  |
| R926736 |  | R950189 |  |
| | | R950216 |  |
| R935117 |  | R950218 |  |

7.3.1100 Synthesis of Intermediates, 2,4-Pyrimidinediamines and 2,4,6-Pyrimidinetriamines According to Schemes VIII and IX

A variety of intermediates and 2,4-pyrimidinediamine compounds were synthesized according to Schemes VIII and IX. Scheme VIII is exemplified by the reaction of 2,4,6-trichloropyrimidine with 3-hydroxyaniline to form a mixture of three compounds, which were separated and purified by chromatography. Scheme IX is exemplified by the reaction of 2,4,5,6-tetrachloridepyrimidine with 3,4-ethylenedioxyaniline to form a mixture of three compounds, which were separated and purified by chromatography.

7.3.1101 Reaction of 2,4,6-trichloropyrimidine with 3-hydroxyaniline**4,6-Dichloro-N2-(3-hydroxyphenyl)-2-pyrimidineamine (R926407)**

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N2,N4-Bis(3-hydroxyphenyl)-6-chloro-2,4-pyrimidinediamine (R926408) and**N2,N4,N6-Tris(3-hydroxyphenyl)-2,4,6-pyrimidinetriamine (R926409)**

A mixture of 2,4,6-trichloroaniline (0.183g, 1 mmol) and 3-hydroxyaniline (0.327g, 3 mmol) in 5 mL MeOH was heated at 100 °C in a sealed vial for 24h. The reaction mixture was diluted with H₂O, acidified with 2N HCl and extracted with EtOAc (3 x 50 mL). Upon removal of solvent the residue was purified by chromatography (as well as preparative TLC) to afford three products, mainly the mono-SNAr, 4,6-dichloro-N2-(3-hydroxyphenyl)-2-pyrimidineamine (R926407), ¹H NMR (CDCl₃): δ 7.16 (t, 1H, J= 8.1 Hz), 6.78 (m, 2H), 6.64 (dd, 1H, J= 1.2 and 8.1 Hz), 6.58 (s, 1H); LCMS: ret. time: 25.08 min.; purity: 99%; MS (m/e): 256 (M⁺); bis-SNAr product, N2,N4-bis(3-hydroxyphenyl)-6-chloro-2,4-pyrimidinediamine (R926408), ¹H NMR (CD₃OD): δ 7.21 (m, 1H), 7.14-7.03 (m, 5H), 6.50 (m, 1H), 6.44 (m, 1H), 6.16 (s, 1H); LCMS: ret. time: 25.14 min.; purity: 99%; MS (m/e): 329 (M⁺); and tris-SNAr product, N2,N4,N6-tris(3-hydroxyphenyl)-2,4,6-pyrimidinetriamine (R926409), ¹H NMR (CD₃OD): δ 7.29 (m, 1H), 7.12-7.05 (m, 5H), 7.02 (m, 2H), 6.88 (dd, 2H, J= 1.2 and 8.1 Hz), 6.46 (dd, 1H, J= 1.5 and 8.1 Hz), 6.41 (dt, 1H); LCMS: ret. time: 20.49 min.; purity: 94%; MS (m/e): 402 (MH⁺).

7.3.1102 N2,N4-Bis(4-methoxycarbonylmethyleneoxyphenyl)-6-chloro-2,4-pyrimidinediamine (R926411)

25

In like manner to the reaction of 2,4,6-trichloropyrimidine with 3-hydroxyaniline, the reaction of 2,4,6-trichloropyrimidine with methyl 4-aminophenoxyacetate gave N2,N4-bis(4-methoxycarbonylmethyleneoxyphenyl)-6-chloro-2,4-pyrimidinediamine. ¹H NMR (CD₃OD): δ 7.65 (bs, 1H), 7.40 (bd, 4H), 6.82 (bd, 4H), 6.00 (s, 1H), 6.62 (bs, 4H), 3.78 (bs, 6H); LCMS: ret. time: 29.87 min.; purity: 98%; MS (m/e): 473 (MH⁺).

30

7.3.1103 Reaction of 2,4,6-trichloropyrimidine with 3,4-ethylenedioxyaniline**4,6-Dichloro-N2-(3,4-ethylenedioxyphenyl)-2-pyrimidineamine (R926515)**

N2,N4-Bis(3,4-ethylenedioxyphenyl)-6-chloro-2,4-pyrimidinediamine (R926245)**N2,N4,N6 -Tris(3,4-ethylenedioxyphenyl)-2,4,6-pyrimidinetriamine (R926516)**

A mixture of 2,4,6-trichloroaniline (1 mmol) and 3,4-ethylenedioxyaniline (3 mmol) in 5 mL MeOH was heated at 100 °C in a sealed vial for 24h. The reaction mixture was diluted with H₂O, acidified with 2N HCl and extracted with EtOAc (3 x 50 mL). Upon removal of solvent the residue was purified by chromatography (as well as preparative TLC) to afford three products, mainly the Mono-SNAr product, 4,6-dichloro-N2-(3,4-ethylenedioxyphenyl)-2-pyrimidineamine (**R926515**). ¹H NMR (CD₃OD): δ 7.05 (s, 1H), 6.83 (m, 2H), 6.45 (bs, 1H), 4.20 (bs, 4H); LCMS: ret. time: 29.75 min.; purity: 96%; MS (m/e): 298 (M⁺); Bis-SNAr product, N2,N4-bis(3,4-ethylenedioxyphenyl)-6-chloro-2,4-pyrimidinediamine (**R926245**):

¹H NMR (CDCl₃): δ 7.23 (d, 1H, J= 3 Hz), 6.90-6.70 (m, 6H), 6.02 (s, 1H), 4.26 (bs, 4H), 4.23 (m, 4H); LCMS: ret. time: 31.34 min.; purity: 95%; MS (m/e): 413 (MH⁺) and Tris-SNAr product, N2,N4,N6 -tris(3,4-ethylenedioxyphenyl)-2,4,6-pyrimidinetriamine (**R926516**)

¹H NMR (CD₃OD): δ 7.16 (d, 1H, J= 3Hz), 7.05 (bd, 1H), 6.99-6.90 (m, 3H), 6.80-6.70 (m, 4H), 6.03 (s, 1H), 4.22 (s, 4H), 4.20 (s, 8H); LCMS: ret. time: 27.72 min.; purity: 61%; MS (m/e): 528 (M⁺).

7.3.1104 Reaction of 2,4,6-trichloropyrimidine with ethyl-4-aminophenoxyacetate**4,6-Dichloro-N2-(4-ethoxycarbonylmethyl)-4,6-dichloro-2-pyrimidineamine (R926549)****2,6-Dichloro-N4-(ethoxycarbonylmethyl)-4-pyrimidineamine (R926550)**

A mixture of 2,4,6-trichloroaniline (1 mmol) and ethyl 2-aminoacetate (3 mmol) in 5 mL MeOH was heated at 100 °C in a sealed vial for 24h. The reaction mixture was diluted with H₂O, acidified with 2N HCl and extracted with EtOAc (3 x 50 mL). Upon removal of solvent the residue was purified by chromatography (as well as preparative TLC) to afford three products, mainly the mono-SNAr product, 4,6-dichloro-N2-(4-ethoxycarbonylmethyl)-4,6-dichloro-2-pyrimidineamine (**R926549**). ¹H NMR (CDCl₃): δ 6.67 (s, 1H), 5.85 (bs, 1H), 4.23 (q, 2H, J= 7.2 Hz), 4.19 (s, 2H), 1.29 (t, 3H, J= 7.2 Hz);

LCMS: ret. time: 26.18 min.; purity: 100%; MS (m/e): 250 (MH⁺); and Mono-SNAr product, 2,6-dichloro-N4-(ethoxycarbonylmethyl)-4-pyrimidineamine (**R926550**): ¹H NMR (CDCl₃): d 6.37 (bs, 1H), 4.28 (q, 2H, J = 6.9 Hz), 4.19 (bs, 2H), 1.31 (t, 3H, J = 7.2 Hz)

7.3.1105 6-Chloro-N2-(4-ethoxycarbonylmethyleneoxyphenyl)-N4-(methoxycarbonylmethyl)-2,4-pyrimidinediamine (R926555)

In like manner to the preparation of 4-[N-(L)-phenylalanine ethyl ester]-N2-(3-hydroxyphenyl)-5-ethoxycarbonyl-2-pyrimidineamine, the reaction of ethyl 4-aminophenoxyacetate with methyl 2-aminoacetate gave 6-chloro-N2-(4-ethoxycarbonylmethyleneoxyphenyl)-N4-(methoxycarbonylmethyl)-2,4-pyrimidinediamine. ¹H NMR (CD₃OD): δ 7.40 (d, 2H, J = 8.7 Hz), 6.86 (d, 2H, J = 9.3 Hz), 5.97 (s, 1H), 4.64 (s, 2H), 4.26 (q, 2H, J = 7.2 Hz), 4.14 (q, 2H, J = 6.9 Hz), 4.05 (s, 2H), 1.25 (m, 6H); LCMS: ret. time: 26.21 min.; purity: 93%; MS (m/e): 409 (MH⁺).

7.3.1106 Reaction of 3,4-ethylenedioxyaniline with 2,4,5,6-tetrachloropyrimidine.

N4-(3,4-Ethylenedioxyphenyl)-2,5,6-trichloro-4-pyrimidineamine (R926466)

N2,N4-Bis(3,4-ethylenedioxyphenyl)-5,6-dichloro-2,4-pyrimidinediamine (R926467) and

N4,N6-Bis(3,4-ethylenedioxyphenyl)-2,5-dichloro-4,6-pyrimidinediamine (R926468)

A mixture of 3,4-ethylenedioxyaniline (0.775 g, 5 mmol) and 2,4,5,6-tetrachloropyrimidine (0.434 g, 2 mmol) in the presence of DIPEA (1.043 mL, 6 mmol) in EtOAc (10 mL) was heated at 80 °C for 3 days. The reaction was diluted with water (50 mL), acidified (2N HCl) and extracted with EtOAc (3 x 50 mL). The residue obtained after removal of solvent was chromatographed using 5-30% EtOAc/hexanes to obtain three products viz. N4-(3,4-Ethylenedioxyphenyl)-2,5,6-trichloro-4-pyrimidineamine (**R926466**): ¹H NMR (CDCl₃): δ 7.18 (d, 1H, J = 2.7 Hz), 6.92 (dd, 1H, J = 2.1 and 8.7 Hz), 6.87 (d, 1H, J = 9 Hz); LCMS: ret. time: 33.53 min.; purity: 100%; MS(m/e): 292 (MH⁺); N2,N4-Bis(3,4-ethylenedioxyphenyl)-5,6-dichloro-2,4-pyrimidinediamine (**R926467**): ¹H NMR (CDCl₃): δ 7.11 (d, 1H, J = 2.4 Hz), 7.06 (d, 1H, J = 2.1 Hz), 7.04 (s, 1H), 6.94 (m, 2H), 6.84 (d, 1H, J = 8.1 Hz), 6.76 (bd, 2H, J = 8.7 Hz), 4.27 (bs, 4H), 4.24 (bs, 1H); LCMS: ret. time:

26.54 min.; purity: 87%; MS(m/e): 364 (MH^+); and N4,N6-Bis(3,4-ethylenedioxyphenyl)-2,5-dichloro-4,6-pyrimidinediamine (**R926468**): ^1H NMR (CDCl_3): δ 7.07 (t, 1H, $J=2.4$ Hz), 6.99 (s, 2H), 6.83 (dd, 2H, $J=2.4$ and 8.7 Hz), 6.75 (dd, 2H, $J=1.8$ and 9 Hz), 4.19 (bs, 4H); LCMS: ret. time: 34.70 min.; purity: 99%; MS(m/e): 365 (MH^+).

5 **7.3.1107 Reaction of 2,4,5,6-tetrachloropyrimidine with ethyl-4-aminophenoxyacetate**

N4-(4-Ethoxycarbonylmethyleneoxyphenyl)-2,5,6-trichloro-4-pyrimidineamine (R926568)

10 **N2,N4-Bis(4-ethoxycarbonylmethyleneoxyphenyl)-5,6-dichloro-2,4-pyrimidinediamine (R926569)**

N2,N5-Bis(4-ethoxycarbonylmethyleneoxyphenyl)-2,5-pyrimidinediamine (R926570)

In like manner to the reaction of 2,4,6-trichloropyrimidine with 3,4-ethylenedioxyaniline, the reaction of 2,4,5,6-tetrachloropyrimidine with ethyl 4-aminophenoxyacetate gave a mixture of mono-SNAr product, N4-(4-ethoxycarbonylmethyleneoxyphenyl)-2,5,6-trichloro-4-pyrimidineamine (**R926568**): ^1H NMR (CDCl_3): δ 7.46 (dd, 2H, $J=2.4$ and 6.9 Hz), 7.3 (s, 1H), 6.95 (dd, 2H, $J=2.4$ and 6.9 Hz), 4.63 (s, 2H), 4.28 (q, 2H, $J=7.2$ Hz), 1.30 (t, 3H, $J=7.2$ Hz); LCMS: ret. time: 30.62 min.; purity: 99%; MS (m/e): 378 (MH^+); Bis-SNAr product, N2,N4-bis((4-ethoxycarbonylmethyleneoxyphenyl)-5,6-dichloro-2,4-pyrimidinediamine (**R926569**): ^1H NMR (CDCl_3): δ 7.42 (d, 2H, $J=9$ Hz), 7.35 (d, 2H, $J=8.7$ Hz), 6.90 (d, 2H, $J=9\text{Hz}$), 6.83 (d, 2H, $J=8.7$ Hz), 4.67 (s, 2H), 4.60 (s, 2H), 4.28 (2q, 4H, $J=4.8$ Hz), 1.31 (2t, 6H, $J=6.3$ Hz); LCMS: ret. time: 33.09 min.; purity: 85%; MS (m/e): 537 (MH^+) and Bis-SNAr product, N2,N5-bis((4-ethoxycarbonylmethyleneoxyphenyl)-2,5-pyrimidinediamine (**R926570**): ^1H NMR (CDCl_3): δ 7.45 (d, 4H, $J=8.7$ Hz), 6.92 (d, 4H, $J=9\text{Hz}$), 6.85 (s, 1H), 4.61 (s, 4H), 4.26 (q, 4H, $J=6.9$ Hz), 1.30 (t, 6H, $J=7.2$ Hz); LCMS: ret. time: 31.66 min.; purity: 97%; MS (m/e): 535 (MH^+).

7.3.1108 Reaction of 2,4,5,6-tetrachloropyrimidine with tert-Butyl-4-aminophenoxyacetate, N4-(4-tert-Butoxyoxycarbonylmethyleneoxyphenyl)-2,5,6-trichloro-4-pyrimidineamine (R926575), N2,N4-Bis(4-tert-butoxyoxycarbonylmethyleneoxyphenyl)-5,6-dichloro-2,4-pyrimidinediamine (R926576) and N4,N6-Bis(4-tert-butoxyoxycarbonylmethyleneoxyphenyl)-2,5-dichloro-4,6-pyrimidinediamine (R926577)

In like manner to the reaction of 2,4,6-trichloropyrimidine with 3,4-ethylenedioxyaniline, the reaction of 2,4,5,6-tetrachloropyrimidine with tert-butyl-4-aminophenoxyacetate gave a mixture of mono-SNAr product, N4-(4-tert-butoxyoxycarbonyl methyleneoxyphenyl)-2,5,6-trichloro-4-pyrimidineamine (**R926575**): ¹H NMR (CDCl₃): δ 7.45 (dd, 2H, J= 2.4 and 7.2 Hz), 6.93 (dd, 2H, J= 2.4 and 7.2 Hz), 4.52 (s, 2H); LCMS: ret. time: 32.56 min.; purity: 100%; MS (m/e): 402 (MH⁺); Bis-SNAr product, N2,N4-bis(4-tert-butoxyoxycarbonylmethyleneoxyphenyl)-5,6-dichloro-2,4-pyrimidinediamine (**R926576**): ¹H NMR (CDCl₃): δ 7.42 (d, 2H, J= 9 Hz), 7.35 (d, 2H, 9.3 Hz), 7.08 (s, 1H), 6.90 (d, 2H, J= 9.3 Hz), 6.82 (d, 2H, J= 8.7 Hz), 4.53 (s, 2H), 4.49 (s, 2H), 1.50 (s, 9H), 1.49 (s, 9H); LCMS: ret. time: 36.04 min.; purity: 92%; MS (m/e): 591 (MH⁺) and Bis-SNAr product, N4,N6-bis(4-tert-butoxyoxycarbonylmethyleneoxyphenyl)-2,5-dichloro-4,6-pyrimidinediamine (**R926577**): ¹H NMR (CDCl₃): δ 7.43 (d, 4H, J= 8.7 Hz), 6.90 (dd, 4H, J= 9.3 Hz), 4.50 (s, 2H), 1.49 (s, 18H); LCMS: ret. time: 35.31 min.; purity: 100%; MS (m/e): 591 (MH⁺).

7.3.1109 Reaction of 2,4,5,6-tetrachloropyrimidine with 3-hydroxyaniline, N4-(3-Hydroxyphenyl)-2,5,6-trichloro-4-pyrimidineamine (R926590), N2,N4-Bis(3-hydroxyphenyl)-5,6-dichloro-2,4-pyrimidinediamine (R926591) and N4,N6-Bis(3-hydroxyphenyl)-2,5-dichloro-4,6-pyrimidinediamine (R926592)

In like manner to the reaction of 2,4,6-trichloropyrimidine with 3,4-ethylenedioxyaniline, the reaction of 2,4,5,6-tetrachloropyrimidine with tert-butyl-4-aminophenoxyacetate gave a mixture of mono-SNAr product, N4-(3-hydroxyphenyl)-2,5,6-trichloro-4-pyrimidineamine (**R926590**): ¹H NMR (CDCl₃): δ 7.38 (bs, 1H), 7.32 (t, 1H, J= 2.4 Hz), 7.22 (s, 1H), 7.01 (dd, 1H, J= 1.2 and 8.1 Hz), 6.68 (dd, 1H, J= 1.8 and 8.1 Hz); LCMS: ret. time: 26.09 min.; purity: 99%; MS (m/e): 292 (MH⁺); Bis-SNAr product, N2,N4-bis(3-hydroxyphenyl)-5,6-dichloro-2,4-pyrimidinediamine (**R926591**): ¹H NMR

(CDCl₃): δ 7.45 (s, 1H), 7.30 (t, 1H, J= 2.4 Hz), 7.18 (t, 1H, J= 2.4 Hz), 7.07 (t, 1H, j= 6.6 Hz), 6.98 (t, 1H, J= 8.1 Hz), 6.75 (m, 2H), 6.54 (dd, 1H, J= 2.4 and 8.1 Hz); LCMS: ret. time: 26.54 min.; purity: 87%; MS (m/e): 364 (MH⁺); and Bis-SNAr product, N₄,N₆-bis(3-hydroxyphenyl)-2,5-dichloro-4,6-pyrimidinediamine (**R926592**): ¹H NMR (CDCl₃): δ 7.34 (t, 2H, j= 2.4 Hz), 7.21 (t, 2H, J= 7.5 Hz), 6.98 (m, 4H), 6.60 (m, 2H); LCMS: ret. time: 25.38 min.; purity: 73%; MS (m/e): 364 (MH⁺).

7.3.1110 N₂,N₄-Bis(3-hydroxyphenyl)-5-chloro-6-thiomethyl-2,4-pyrimidinediamine (R926595)

The reaction of N₂ N₄-bis(3-hydroxyphenyl)-5,6-dichloro-2,4-pyrimidinediamine (18 mg, 0.05 mmol) with sodium thiomethoxide (10 mg, 0.15 mmol) in absolute EtOH (1 mL) was heated at 80 °C for 3 days, diluted with H₂O, extracted with EtOAc (3 x 10 mL), and solvent was evaporated to obtain the N₂ N₄-bis(3-hydroxyphenyl)-5-chloro-6-thiomethyl-2,4-pyrimidinediamine (**R926595**). ¹H NMR (CD₃OD): δ 7.40-7.2 (m, 2H), 7.20-6.80 (m, 3H), 6.67 (m, 1H), 6.45-6.30 (m, 2H), 2.4 (s, 3H); LCMS: ret. time: 27.78 min.; purity: 80%; MS (m/e): 376 (MH⁺).

7.3.1111 N₂,N₄-Bis(3,4-ethylenedioxyphenyl)-5-chloro-6-thiomethyl-2,4-pyrimidinediamine (R926475)

In like manner to the preparation of N₂ N₄-bis(3-hydroxyphenyl)-5-chloro-6-thiomethyl-2,4-pyrimidinediamine (**R926595**), the reaction of N₂,N₄-bis(3,4-ethylenedioxyphenyl)-5,6-dichloro-2,4-pyrimidinediamine gave N₂,N₄-bis(3,4-ethylenedioxyphenyl)-5-chloro-6-thiomethyl-2,4-pyrimidinediamine. ¹H NMR (CDCl₃): δ 7.10 (bd, 2H), 7.00-6.00 (m, 4H), 4.23 (s, 4H), 4.10 (s, 4H), 2.60 (s, 3H); LCMS: ret. time: 36.14 min; purity: 100%; MS (m/e): 459 (MH⁺).

7.3.1112 6-Chloro N₄-(3-hydroxyphenyl)-4-pyrimidineamine (R926530)

The reaction of 4,6-dichloropyrimidine with excess 3-hydroxyaniline in MeOH at 80 °C for 24 h followed by dilution with water and acidification gave the crude product which was purified by silica gel column chromatography to obtain 6-chloro N₄-(3-hydroxyphenyl)-4-pyrimidineamine. ¹H NMR (CD₃OD): δ 8.36 (d, 1H, J= 1.2 Hz), 7.15 (t, 1H, J= 8.4 Hz), 6.93 (dd, 1.2 and 8.1 Hz), 6.74 (d, 1H, J= 1.2 Hz), 6.55 (dd, 1.8 and 8.1 Hz); LCMS (m/e): ret. time: 19.75 min.; purity: 99%; MS (m/e): 222 (MH⁺).

7.3.1113 N2,N4-Bis(3,4-ethylenedioxyphenyl)-5-phenyl-2,4-pyrimidinediamine (R925784)

A mixture of N2,N4-bis(3,4-ethylenedioxyphenyl)-5-bromo-2,4-pyrimidinediamine (20 mg, 0.044 mmol) and phenylboronic acid (6.9 mg, 0.057 mmol) in DME (1 mL) was prepared in a sealed tube and purged with N₂. Tetrakis(triphenylphosphine) palladium(0) (0.002 mmol) was added, and the reaction tube sealed and heated at 80 °C overnight. After cooling, the reaction mixture was diluted with EtOAc, washed with 1N NaOH and brine, dried (MgSO₄), and concentrated. The residue was purified by preparative TLC (40% EtOAc/hexanes) to afford N2,N4-bis(3,4-ethylenedioxyphenyl)-5-phenyl-2,4-pyrimidinediamine. ¹H NMR (CD₃OD): δ 7.77 (s, 1H), 7.52-7.36 (m, 5H), 7.10 (d, 1H, J= 2.4 Hz), 7.05 (d, 1H, J= 2.4 Hz), 6.93 (dd, 1H, J= 2.4 and 8.7 Hz), 6.87 (dd, 1H, J= 2.4 and 8.7 Hz), 6.73 (d, 1H, J= 8.7 Hz), 6.69 (d, 1H, J= 8.7 Hz), 4.23-4.20 (m, 8H); LCMS: ret. time: 25.38 min.; purity: 100 %; MS (m/e): 455 (MH⁺).

7.3.1114 N2,N4-Bis(3,4-ethylenedioxyphenyl)-5-(2-furanyl)-2,4-pyrimidinediamine (R925785)

In a manner similar to the preparation of N2,N4-bis(3,4-ethylenedioxyphenyl)-5-phenyl-2,4-pyrimidinediamine, N2,N4-bis(3,4-ethylenedioxyphenyl)-5-bromo-2,4-pyrimidinediamine and furan-2-boronic acid were reacted to yield N2,N4-bis(3,4-ethylenedioxyphenyl)-5-(2-furanyl)-2,4-pyrimidinediamine. ¹H NMR (CD₃OD): δ 8.13 (s, 1H), 7.61 (d, 1H, J=1.8 Hz), 7.12 (d, 1H, J= 2.4 Hz), 7.08 (d, 1H, J= 2.4 Hz), 6.93 (td, 2H, J= 2.4 and 8.7 Hz), 6.78 (d, 1H, J= 8.7 Hz), 6.68 (d, 1H, J= 8.7 Hz), 6.58 (d, 1H, J= 2.4 Hz), 6.54 (dd, 1H, J= 1.8 and 3.6), 4.24 (s, 4H), 4.20 (bs, 4H); LCMS: ret. time: 15.03 min.; purity: 88 %; MS (m/e): 445 (MH⁺).

7.3.1115 N2,N4-Bis(3,4-ethylenedioxyphenyl)-5-(4-chlorophenyl)-2,4-pyrimidinediamine (R925786)

In a manner similar to the preparation of N2,N4-bis(3,4-ethylenedioxyphenyl)-5-phenyl-2,4-pyrimidinediamine, N2,N4-bis(3,4-ethylenedioxyphenyl)-5-bromo-2,4-pyrimidinediamine and 4-chlorophenylboronic acid were reacted to yield N2,N4-bis(3,4-ethylenedioxyphenyl)-5-(4-chlorophenyl)-2,4-pyrimidinediamine. ¹H NMR (DMSO-d₆): δ 8.99 (bs, 1H), 8.05 (bs, 1H), 7.85 (s, 1H), 7.50-7.42 (m, 4H), 7.23 (bs, 1H), 7.10 (dd, 1H, J= 2.4 and 8.7 Hz), 7.06 (t, 1H, J= 2.4 Hz), 7.00-6.94 (m, 1H), 6.73 (d, 1H, J= 8.7 Hz), 6.63 (d, 1H, J= 8.7 Hz); LCMS: ret. time: 16.12 min.; purity: 86 %; MS (m/e): 490 (MH⁺).

7.3.1116 N2,N4-Bis(3,4-ethylenedioxyphenyl)-5-(3-chlorophenyl)-2,4-pyrimidinediamine (R925787)

In a manner similar to the preparation of N2,N4-bis(3,4-ethylenedioxyphenyl)-5-phenyl-2,4-pyrimidinediamine, N2,N4-bis(3,4-ethylenedioxyphenyl)-5-bromo-2,4-pyrimidinediamine and 3-chlorophenylboronic acid were reacted to yield N2,N4-bis(3,4-ethylenedioxyphenyl)-5-(3-chlorophenyl)-2,4-pyrimidinediamine. ¹H NMR (CD₃OD): δ 7.77 (s, 1H), 7.45-7.41 (m, 2H), 7.38-7.33 (m, 2H), 7.09 (d, 1H, J= 2.4 Hz), 7.01 (d, 1H, J= 2.4 Hz), 6.92 (dd, 1H, J= 2.4 and 9.0 Hz), 6.86 (dd, 1H, J= 2.4 and 8.7 Hz), 6.74 (d, 1H, J= 8.7 Hz), 6.67 (d, 1H, J= 8.7 Hz), 4.21 (s, 4H), 4.19 (s, 4H); LCMS: ret. time: 27.18 min.; purity: 95 %; MS (m/e): 490 (MH⁺).

7.3.1117 N2,N4-Bis(3,4-ethylenedioxyphenyl)-5-(4-methoxycarbonylphenyl)-2,4-pyrimidinediamine (R925813)

In a manner similar to the preparation of N2,N4-bis(3,4-ethylenedioxyphenyl)-5-phenyl-2,4-pyrimidinediamine, N2,N4-bis(3,4-ethylenedioxyphenyl)-5-bromo-2,4-pyrimidinediamine and (4-methoxycarbonylphenyl)boronic acid were reacted to yield N2,N4-bis(3,4-ethylenedioxyphenyl)-5-(4-methoxycarbonylphenyl)-2,4-pyrimidinediamine. LCMS: ret. time: 26.35 min.; purity: 90 %; MS (m/e): 514 (MH⁺).

7.3.1118 N2,N4-Bis(3,4-ethylenedioxyphenyl)-5-(4-hydroxyphenyl)-2,4-pyrimidinediamine (R925816)

In a manner similar to the preparation of N2,N4-bis(3,4-ethylenedioxyphenyl)-5-phenyl-2,4-pyrimidinediamine, N2,N4-bis(3,4-ethylenedioxyphenyl)-5-bromo-2,4-pyrimidinediamine and 4-hydroxyphenylboronic acid were reacted to yield N2,N4-bis(3,4-ethylenedioxyphenyl)-5-(4-hydroxyphenyl)-2,4-pyrimidinediamine. ¹H NMR (DMSO-d₆): δ 9.53 (s, 1H), 8.92 (s, 1H), 7.78 (s, 1H), 7.74 (bs, 1H), 7.24 (bs, 1H), 7.22 (d, 2H, J= 8.7 Hz), 7.12-7.09 (m, 2H), 6.97 (dt, 1H, J= 2.4 and 8.7 Hz), 6.83 (d, 2H, J= 8.4 Hz), 6.72 (d, 1H, J= 8.1 Hz), 6.62 (d, 1H, J= 9.0 Hz), 4.19 (s, 4H), 4.17 (s, 4H); LCMS: ret. time: 23.51 min.; purity: 95 %; MS (m/e): 471 (MH⁺).

7.3.1119 N2,N4-Bis(3-hydroxyphenyl)-5-phenyl-2,4-pyrimidinediamine (R925783)

In a manner similar to the preparation of N2,N4-bis(3,4-ethylenedioxyphenyl)-5-phenyl-2,4-pyrimidinediamine, N2,N4-bis(3-hydroxyphenyl)-5-bromo-2,4-pyrimidinediamine and phenylboronic acid were reacted to yield N2,N4-bis(3-

hydroxyphenyl)-5-phenyl-2,4-pyrimidinediamine. ^1H NMR (CD_3OD): δ 7.85 (bs, 1H), 7.54-7.38 (m, 5H), 7.13-7.11 (m, 2H), 7.10-7.04 (m, 3H), 6.97 (dt, 1H, J = 1.8 and 8.1 Hz), 6.54 (ddd, 1H, J = 1.9, 2.4, and 7.2 Hz), 6.44 (dt, 1H, J = 1.8 and 6.0 Hz); LCMS: ret. time: 20.66 min.; purity: 96 %; MS (m/e): 371 (MH^+).

5 **7.3.1120 N2,N4-Bis(3-hydroxyphenyl)-5-(3,4-methylenedioxyphenyl)-2,4-pyrimidinediamine (R925788)**

In a manner similar to the preparation of N2,N4-bis(3,4-ethylenedioxyphenyl)-5-phenyl-2,4-pyrimidinediamine, N2,N4-bis(3-hydroxyphenyl)-5-bromo-2,4-pyrimidinediamine and 3,4-methylenedioxyphenylboronic acid were reacted to yield
10 N2,N4-bis(3-hydroxyphenyl)-5-(3,4-methylenedioxyphenyl)-2,4-pyrimidinediamine. ^1H NMR (CD_3OD): δ 7.82 (s, 1H), 7.13-7.06 (m, 3H), 7.04-7.01 (m, 2H), 6.97 (dt, 1H, J = 1.2 and 8.7 Hz), 6.94-6.88 (m, 3H), 6.52 (ddd, 1H, J = 1.2, 2.4, and 6.9 Hz), 6.42 (dt, 1H, J = 2.1 and 7.5 Hz), 6.01 (s, 2H); LCMS: ret. time: 21.11 min.; purity: 99 %; MS (m/e): 415 (MH^+).

15 **7.3.1121 N2,N4-Bis(3,4-ethylenedioxyphenyl)-6-phenyl-2,4-pyrimidinediamine (R925811)**

In a manner similar to the preparation of N2,N4-bis(3,4-ethylenedioxyphenyl)-5-phenyl-2,4-pyrimidinediamine, N2,N4-bis(3,4-ethylenedioxyphenyl)-6-chloro-2,4-pyrimidinediamine and phenylboronic acid were reacted to yield N2,N4-bis(3,4-ethylenedioxyphenyl)-6-phenyl-2,4-pyrimidinediamine. ^1H NMR (CD_3OD): δ 7.97-7.92
20 (m, 2H), 7.46-7.43 (m, 3H), 7.35 (d, 1H, J = 2.7 Hz), 7.19 (d, 1H, J = 2.4 Hz), 7.07-7.00 (m, 2H), 6.75 (t, 2H, J = 8.7 Hz), 6.50 (s, 1H), 4.24-4.19 (m, 8H); LCMS: ret. time: 26.68 min.; purity: 97 %; MS (m/e): 455 (MH^+).

7.3.1122 N2,N4-Bis(3-hydroxyphenyl)-6-phenyl-2,4-pyrimidinediamine (R925812)

25 In a manner similar to the preparation of N2,N4-bis(3,4-ethylenedioxyphenyl)-5-phenyl-2,4-pyrimidinediamine, N2,N4-bis(3-hydroxyphenyl)-6-chloro-2,4-pyrimidinediamine and phenylboronic acid were reacted to yield N2,N4-bis(3-hydroxyphenyl)-6-phenyl-2,4-pyrimidinediamine. LCMS: ret. time: 22.13 min.; purity: 90 %; MS (m/e): 371 (MH^+).

7.3.1123 N2-(3-Aminocarbonylmethyleneoxyphenyl)-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R926747)

The hydrolysis of N2-(3-cyanomethyleneoxyphenyl)-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine gave N2-(3-aminocarbonylmethyleneoxyphenyl)-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine. LCMS: ret. time: 16.76 min.; purity: 93 %; MS (m/e): 412 (MH⁺).

7.3.1124 N2,N4-Bis(3-sodiumphenoxy)-5-fluoro-2,4-pyrimidinediamine (R926461)

The reaction of N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine with 2 equivalents of sodium methoxide in methanol gave the requisite compound, N2,N4-bis(3-sodiumphenoxy)-5-fluoro-2,4-pyrimidinediamine. ¹H NMR (D₂O): δ 7.65 (bd, 1H), 7.00-6.90 (m, 2H), 6.71 (m, 2H), 6.55 (dd, 1H, J= 1.2 and 6.3 Hz), 6.31 (bd, 1H, J= 8.1 Hz), 6.23 (bd, 1H, J= 8.7 Hz); ¹⁹F NMR (D₂O): - 47016; LCMS: ret. time: 15.68 min.; purity: 99%; MS (m/e): 313 (MH⁺).

7.3.1125 5-Fluoro-N4-(3-hydroxyphenyl)-N2-[4-(1,4,5,6-tetrahydro-2-pyrimidyl)methyleneoxyphenyl]-2,4-pyrimidinediamine (R945169)

The reaction of N2-(4-cyanomethyleneoxyphenyl)-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine and HCl in ethanol, followed by 1,3-diaminopropane in methanol at 100 °C gave 5-fluoro-N4-(3-hydroxyphenyl)-N2-[4-(1,4,5,6-tetrahydro-2-pyrimidyl)methyleneoxyphenyl]-2,4-pyrimidinediamine. ¹H NMR (CD₃OD): δ 2.05 (p, J= 5.7 Hz, 2H), 3.49 (t, J= 5.7 Hz, 4H), 4.84 (s, 2H), 6.56 (ddd, J= 2.1, 3.6 and 5.4 Hz, 1H), 6.93 (d, J= 9.0 Hz, 2H), 7.11-7.13 (m, 2H), 7.21 (m, 1H), 7.55 (d, J= 9.0 Hz, 2H), 7.87 (d, J= 3.9 Hz, 1H); ¹⁹F NMR (282 MHz, CD₃OD): δ - 168.66; LCMS: ret. time: 12.77 min.; purity: 97.61%; MS (m/e): 409.08 (MH⁺).

7.3.1126 5-Fluoro-N4-(3-hydroxyphenyl)-N2-[4-[(4,4-dimethyl-3-oxazolin-2-yl)methyleneoxy]phenyl]-2,4-pyrimidinediamine (R926702)

N2-[4-(cyanomethyleneoxy)phenyl]-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine and 2-amino-2-methylpropanol were reacted to yield 5-fluoro-N4-(3-hydroxyphenyl)-N2-[4-[(4,4-dimethyl-3-oxazolin-2-yl)methyleneoxy]phenyl]-2,4-pyrimidinediamine. ¹H NMR (CDCl₃): δ 7.87 (d, 1H, J= 3.6 Hz), 7.37 (t, 1H, J= 2.4 Hz),

7.34 (d, 2H, J= 9.0 Hz), 7.14 (t, 1H, J= 8.1 Hz), 6.94 (bs, 1H), 6.90 (d, 2H, J= 9.0 Hz), 6.78 (dd, 1H, J= 2.4 and 8.4 Hz), 6.74 (d, 1H, J= 3.0 Hz), 6.62 (ddd, 1H, J= 1.2, 2.4, and 8.4 Hz), 4.67 (s, 2H), 4.02 (s, 2H), 1.25 (s, 6H); ¹⁹F NMR (CDCl₃): -47399; LCMS: ret. time: 13.82 min.; purity: 98%; MS (m/e): 425 (M+2H).

5 **7.3.1127 N4-(3-Carboxy-4-hydroxyphenyl)-5-fluoro-N2-[3-ethoxycarbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R950290)**

10 A mixture of equimolar amounts of 2-chloro-N4-(3-carboxy-4-hydroxyphenyl)-5-fluoro-4-aminopyridine and 3-ethoxycarbonylmethyleneoxyaniline in MeOH in a pressure tube at 110°C for 24h or in EtOH using microwave at 175°C for 10-20 min followed by aqueous work up gave N4-(3-carboxy-4-hydroxyphenyl)-5-fluoro-N2-[3-ethoxycarbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. LCMS: purity: 97.8%; MS (m/e): 443.20 (MH⁺).

15 **7.3.1128 N4-(3-Carboxy-4-hydroxyphenyl)-5-fluoro-N2-[3-carboxymethyleneoxyphenyl]-2,4-pyrimidinediamine (R950291)**

20 The reaction of N4-(3-carboxy-4-hydroxyphenyl)-5-fluoro-N2-[3-ethoxycarbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (0.1 g) and LiOH (10 equivalents) in MeOH:water (1:1, v/v) for 1h at room temperature followed by treatment with aqueous HCl gave the solid. The resulting solid was filtered, washed with water and dried to give N4-(3-carboxy-4-hydroxyphenyl)-5-fluoro-N2-[3-carboxymethyleneoxyphenyl]-2,4-pyrimidinediamine. LCMS: purity: 91.5%; MS (m/e): 415.16 (MH⁺).

25 **7.3.1129 N4-(3-Methoxycarbonyl-4-hydroxyphenyl)-5-fluoro-N2-[3-ethoxycarbonyl methyleneoxyphenyl]-2,4-pyrimidinediamine (R950293)**

30 A solution of N4-(3-carboxy-4-hydroxyphenyl)-5-fluoro-N2-[3-ethoxycarbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine in dry MeOH was treated with a 4 M solution of HCl in dioxane. The mixture was stirred for 1 hour at 22°C, concentrated to dryness and purified by flash chromatography on silica gel to give N4-(3-methoxycarbonyl-4-hydroxyphenyl)-5-fluoro-N2-[3-ethoxycarbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine as a white solid. ¹H NMR (DMSO): δ 10.30 (s, 1H), 10.13 (s, 1H), 8.22 (d, 1H, J= 5.3 Hz), 7.96 (d, 1H, J= 2.4 Hz), 7.71 (dd, J = 2.4, 9.0 Hz, 1H), 6.95-7.11

(m, 4H), 6.51 (m, 1H), 4.56 (s, 2H), 4.09 (q, J = 7.2 Hz, 2H), 3.72 (s, 3H), 1.14 (t, J = 7.2 Hz, 3H); LCMS: purity: 96.8%; MS (m/e): 457.25 (MH⁺).

7.3.1130 N4-(4-Methoxy-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-ethoxycarbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R950294)

A mixture of equimolar amounts of 2-chloro-N4-(4-methoxy-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-4-aminopyridine and 3-ethoxycarbonylmethyleneoxyaniline in EtOH using microwave at 175°C for 10-20 min followed by aqueous work up gave N4-(4-methoxy-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-ethoxycarbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. LCMS: purity: 92.1%; MS (m/e): 469.26 (MH⁺).

7.3.1131 N4-(4-Methoxy-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-methoxycarbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R950295)

A mixture of equimolar amounts of 2-chloro-N4-(4-methoxy-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-4-aminopyridine and 3-ethoxycarbonylmethyleneoxyaniline in MeOH in a pressure tube at 110°C for 24h followed by aqueous work up gave N4-(4-methoxy-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-methoxycarbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. LCMS: purity: 87.6%; MS (m/e): 455.26 (MH⁺).

7.3.1132 N4-(4-Ethoxy-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-(N-methylamino) carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R950296)

A solution of N4-(4-ethoxy-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-ethoxycarbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine in EtOH was treated with the HCl salt of methylamine. The mixture was stirred for 4 hours at 100°C, concentrated to dryness and purified by flash chromatography on silica gel to give N4-(4-ethoxy-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine as a white solid. LCMS: purity: 87.4%; MS (m/e): 468.29 (MH⁺).

7.3.1133 N4-(4-Carboxyethyleneoxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R950344)

A mixture of equimolar amounts of 2-chloro-N4-(4-carboxyethyleneoxyphenyl)-5-fluoro-4-aminopyridine and 3-(N-methylamino)carbonylmethyleneoxyaniline in MeOH in a pressure tube at 110°C for 24h or in EtOH using microwave at 175°C for 10-20 min followed by aqueous work up gave N4-(4-carboxyethyleneoxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. LCMS: purity: 97.8%; MS (m/e): 456.32 (MH⁺).

7.3.1134 N4-(2,3-Dihydro-4-benzopyranon-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R950345)

A solution of N4-(4-Methoxycarbonylethyleneoxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine in TFOH was heated for 2 hours at 100°C. Aqueous work up followed by flash chromatography on silica gel gave N4-(2,3-dihydro-4-benzopyranon-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine as a white solid. LCMS: purity: 92.2%; MS (m/e): 435.95 (MH⁺).

7.3.1135 N4-(4-Methoxycarbonylethyleneoxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R950346)

A solution of N4-(4-carboxyethyleneoxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine in dry MeOH was treated with a 4 M solution of HCl in dioxane. The mixture was stirred for 1 hour at 22°C, concentrated to dryness and purified by flash chromatography on silica gel to give N4-(4-methoxycarbonylethyleneoxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine as a white solid. LCMS: purity: 85.2%; MS (m/e): 468.01 (MH⁺).

7.3.1136 N4-(4-Hydroxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R950347)

The reaction of N4-(4-methoxycarbonylethyleneoxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine and LiOH (10

equivalents) in MeOH:water (1:1, v/v) for 1h at room temperature followed by treatment with aqueous HCl gave a pale yellow solid. The resulting solid was filtered, washed with water and dried to give N4-(4-hydroxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. LCMS: purity: 94.7%; MS (m/e): 382.03 (MH⁺).

7.3.1137 N4-(2,3-Dihydro-4-oxime-benzopyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R950348)

A mixture N4-(2,3-dihydro-4-benzopyranon-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine and hydroxylamine (20 equivalents) in pyridine at 22°C for 16 hours followed by aqueous work up gave N4-(2,3-dihydro-4-oxime-benzopyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine as a white solid. LCMS: purity: 89.5%; MS (m/e): 451.00 (MH⁺).

7.3.1138 N4-(4-Hydroxy-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R950349)

A solution of N4-(2,3-dihydro-4-benzopyranon-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine in dry MeOH was treated with a sodiumcyanoborohydride. The mixture was stirred for 1 hour at 22°C, concentrated to dryness and purified by flash chromatography on silica gel to give N4-(4-Hydroxy-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine as a white solid. ¹H NMR (DMSO): δ 9.19 (s, 1H), 9.09 (s, 1H), 8.03 (d, 1H, J = 2.4 Hz), 7.28-7.93 (m, 5H), 7.07 (t, 1H, J = 7.2 Hz), 6.71 (d, 1H, J = 7.2 Hz), 6.44 (dd, 1H, J = 2.6, 7.2 Hz), 5.31 (d, 1H, J = 5.1 Hz), 4.14-4.59 (m, 3H), 4.30 (s, 2H), 2.63 (d, 3H, J = 4.8 Hz), 1.82-2.03 (m, 2H); LCMS: purity: 93.3%; MS (m/e): 440.15 (MH⁺).

7.3.1139 N4-(2,3-Dihydro-4-O-methyloxime-benzopyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R950356)

A mixture N4-(2,3-dihydro-4-benzopyranon-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine and methoxyamine (20 equivalents) in pyridine at 22°C for 16 hours followed by aqueous work up gave N4-(2,3-

dihydro-4-oxime-benzopyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine as a white solid.
LCMS: purity: 85.5%; MS (m/e): 465.10 (MH⁺).

7.3.1140 N4-(4-Amino-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R950368)

A mixture N4-(4-azido-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine and Pd/C (10%) in MeOH was hydrogenated at 22°C for 6 hours (40psi). The mixture was filtered and concentrated to dryness to give N4-(4-amino-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine as a white solid. ¹H NMR (DMSO): δ 9.60 (s, 1H), 9.46 (s, 1H), 8.73 (bs, 3H), 8.00-8.10 (m, 3H), 7.47 (s, 1H), 7.42 (m, 1H), 7.29 (d, 1H, J = 7.2 Hz), 7.11 (t, 1H, J = 7.2 Hz), 6.82 (d, 1H, J 7.0 Hz), 6.46 (m, 1H), 4.23-4.46 (m, 3H), 4.31 (s, 3H), 2.63 (d, 3H, J = 4.8 Hz), 2.09-2.29 (m, 2H); LCMS: purity: 97.6%; MS (m/e): 438.98 (MH⁺).

7.3.1141 N4-(3-Methylcarbonylphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R950371)

A mixture of equimolar amounts of 2-chloro-N4-(3-methylcarbonylphenyl)-5-fluoro-4-aminopyridine and 3-(N-methylamino)carbonylmethyleneoxyaniline in MeOH in a pressure tube at 110°C for 24h or in EtOH using microwave at 175°C for 10-20 min followed by aqueous work up gave N4-(3-methylcarbonylphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine as a white solid. ¹H NMR (DMSO): δ 10.16 (s, 1H), 9.82 (s, 1H), 8.24 (d, 1H, J= 2.4 Hz), 8.15 (s, 1H), 7.91-8.07 (m, 2H), 7.70 (d, 1H, J= 7.0 Hz), 7.49 (t, 1H, J = 7.2 Hz), 7.08-7.21 (m, 3H), 6.56 (d, 1H, J = 7.2 Hz), 4.30 (s, 3H), 2.62 (d, 3H, J = 4.8 Hz), 2.48 (s, 3H); LCMS: purity: 93.8%; MS (m/e): 410.50 (MH⁺).

7.3.1142 N4-(3-Phenylcarbonylphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R950372)

A mixture of equimolar amounts of 2-chloro-N4-(3-phenylcarbonylphenyl)-5-fluoro-4-aminopyridine and 3-(N-methylamino)carbonylmethyleneoxyaniline in MeOH in a pressure tube at 110°C for 24h or in EtOH using microwave at 175°C for 10-20 min

followed by aqueous work up gave N4-(3-phenylcarbonylphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine as a white solid. LCMS: purity: 86.0%; MS (m/e): 472.50 (MH⁺).

7.3.1143 N4-(3-Methylcarbonyloximephenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R950373)

A mixture N4-(3-methylcarbonylphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine and hydroxylamine (20 equivalents) in pyridine at 22°C for 16 hours followed by aqueous work up gave N4-(3-methylcarbonyloximephenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine as a white solid. ¹H NMR (DMSO): δ 11.21 (s, 1H), 10.11 (s, 1H), 9.85 (s, 1H), 6.54-8.23 (m, 9H), 4.32 (s, 2H), 2.63 (d, J = 7.0 Hz, 3H), 2.47 (s, 3H); LCMS: purity: 92.4%; MS (m/e): 425.28 (MH⁺).

7.3.1144 N4-(3-Phenylcarbonyloximephenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R950374)

A mixture N4-(3-phenylcarbonylphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine and hydroxylamine (20 equivalents) in pyridine at 22°C for 16 hours followed by aqueous work up gave N4-(3-phenylcarbonyloximephenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine as a white solid. ¹H NMR (DMSO): δ 11.63 (s, 1H), 10.30 (s, 1H), 9.85 (s, 1H), 6.44-8.43 (m, 14H), 4.42 (s, 2H), 2.63 (d, J = 7.0 Hz, 3H); LCMS: purity: 92.4%; MS (m/e): 487.31 (MH⁺).

7.3.1145 N2,N4-Bis(3-methylcarbonylphenyl)-5-fluoro-2,4-pyrimidinediamine (R950376)

A mixture of 2,4-dichloro-5-fluoropyridine and three equivalents of 3-acetophenone in MeOH in a pressure tube at 110°C for 24h or in EtOH using microwave at 175°C for 10-20 min followed by aqueous work up gave N2,N4-bis(3-methylcarbonylphenyl)-5-fluoro-2,4-pyrimidinediamine as a white solid. LCMS: purity: 93.1%; MS (m/e): 365.19 (MH⁺).

7.3.1146 N₂,N₄-Bis(3-phenylcarbonylphenyl)-5-fluoro-2,4-pyrimidinediamine (R950377)

A mixture of 2,4-dichloro-5-fluoropyridine and three equivalents of 3-benzophenone in MeOH in a pressure tube at 110°C for 24h or in EtOH using microwave at 175°C for 10-
5 20 min followed by aqueous work up gave N₂,N₄-bis(3-phenylcarbonylphenyl)-5-fluoro-2,4-pyrimidinediamine as a white solid. LCMS: purity: 95.7%; MS (m/e): 489.29 (MH⁺).

7.3.1147 N₂,N₄-Bis(2,3-dihydro-4-benzopyranon-6-yl)-5-fluoro-2,4-pyrimidinediamine (R950378)

A solution of N₂,N₄-bis(4-methoxycarbonyl ethyleneoxyphenyl)-5-fluoro-2,4-
10 pyrimidinediamine in TFOH was heated for 2 hours at 100°C. Aqueous work up followed by flash chromatography on silica gel gave N₂,N₄-bis(2,3-dihydro-4-benzopyranon-6-yl)-5-fluoro-2,4-pyrimidinediamine as a white solid. ¹H NMR (DMSO): δ 9.36 (s, 1H), 9.14 (s, 1H), 8.06 (d, 1H, J = 2.4 Hz), 7.72-7.99 (m, 3H), 6.97 (d, J = 7.2 Hz, 1H), 6.87 (d, J = 7.2 Hz, 1H), 4.42-4.52 (m, 4H), 2.70-2.78 (m, 4H); LCMS: purity: 94.3%; MS (m/e): 484.50
15 (MH⁺).

7.3.1148 N₂,N₄-Bis(3-methylcarbonyloximephenyl)-5-fluoro-2,4-pyrimidinediamine (R950379)

A mixture of N₂,N₄-bis(3-methylcarbonylphenyl)-5-fluoro-2,4-pyrimidinediamine and hydroxylamine (20 equivalents) in pyridine at 22°C for 16 hours followed by aqueous
20 work up gave N₂,N₄-bis(3-methylcarbonyloximephenyl)-5-fluoro-2,4-pyrimidinediamine as a white solid. ¹H NMR (DMSO): δ 11.21 (s, 1H), 10.11 (s, 1H), 9.85 (s, 1H), 6.54-8.23 (m, 9H), 4.32 (s, 2H), 2.63 (d, J = 7.0 Hz, 3H), 2.47 (s, 3H); LCMS: purity: 92.1%; MS (m/e): 393.06 (M-H).

7.3.1149 N₂,N₄-Bis(3-phenylcarbonyloximephenyl)-5-fluoro-2,4-pyrimidinediamine (R950380)

A mixture of N₂,N₄-bis(3-phenylcarbonylphenyl)-5-fluoro-2,4-pyrimidinediamine and hydroxylamine (20 equivalents) in pyridine at 22°C for 16 hours followed by aqueous
25 work up gave N₂,N₄-bis(3-phenylcarbonyloximephenyl)-5-fluoro-2,4-pyrimidinediamine as a white solid. LCMS: purity: 93.3%; MS (m/e): 486.05 (M-H).

7.3.1150 N2,N4-Bis(2,3-dihydro-4-oxime-benzopyran-6-yl)-5-fluoro-2,4-pyrimidinediamine (R950381)

A mixture of N2,N4-bis(2,3-dihydro-4-benzopyranon-6-yl)-5-fluoro-2,4-pyrimidinediamine and hydroxylamine (20 equivalents) in pyridine at 22°C for 16 hours followed by aqueous work up gave N2,N4-bis(2,3-dihydro-4-oxime-benzopyran-6-yl)-5-fluoro-2,4-pyrimidinediamine as a white solid. LCMS: purity: 98.1%; MS (m/e): 449.03 (M-H⁺).

7.3.1151 N4-(4-Acetyloxy-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R950382)

A solution of N4-(4-hydroxy-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine in pyridine was treated with acetic anhydride at 22°C for 16 hours. Aqueous work up gave N4-(4-acetyloxy-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine as a white solid. ¹H NMR (DMSO): δ 10.43 (bs, 1H), 9.62 (bs, 1H), 8.03 (d, 1H, J = 2.4 Hz), 7.10-7.83 (m, 7H), 6.83 (d, 1H, J = 7.4 Hz), 6.52 (d, 1H, J = 7.2 Hz), 5.01 (m, 1H), 4.75 (s, 2H), 4.03-4.32 (m, 2H), 2.62 (s, 3H), 2.23 (s, 3H), 1.93-2.13 (m, 2H); LCMS: purity: 92.1%; MS (m/e): 393.06 (M-H⁺).

7.3.1152 N4-(4-Azido-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R950383)

A solution of N4-(4-hydroxy-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine in dry THF was treated with 2 equivalents of DPPA and DBU. The mixture was stirred for 3 hours at 22°C, concentrated to dryness and purified by flash chromatography on silica gel to give N4-(4-azido-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine as a white solid. ¹H NMR (DMSO): δ 10.09 (bs, 1H), 9.83 (bs, 1H), 8.18 (d, 1H, J = 2.4 Hz), 7.97 (m, 1H), 7.11-7.61 (m, 6H), 6.82 (d, 1H, J = 7.8 Hz), 6.62 (d, 1H, J = 7.2 Hz), 4.78 (s, 2H), 4.03-4.33 (m, 3H), 2.62 (s, 3H), 1.93-2.13 (m, 2H); LCMS: purity: 97.9%; MS (m/e): 463.07 (MH⁺).

7.3.1153 N4-(4-Benzopyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R950385)

A solution of N4-(4-hydroxy-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine in THF was treated with boron trifluoride etherate at 80°C for 8 hours. Aqueous work up gave N4-(4-benzopyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine as a white solid. ¹H NMR (DMSO): δ 9.18 (s, 1H), 9.14 (s, 1H), 8.03 (d, J = 2.4 Hz, 1H), 7.93 (bs, 1H), 5.86-7.48 (m, 9H) 4.73-4.74 (m, 2H), 4.33 (s, 2H), 2.62 (s, 3H); LCMS: purity: 96.5%; MS (m/e): 420.07 (M-H⁺).

7.3.1154 N4-(3-Hydroxymethylen-4-methoxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R950386)

A mixture of equimolar amounts of 2-chloro-N4-(3-hydroxymethylen-4-methoxyphenyl)-5-fluoro-4-aminopyridine and 3-(N-methylamino)carbonylmethyleneoxyaniline in MeOH in a pressure tube at 110°C for 24h or in EtOH using microwave at 175°C for 10-20 min followed by aqueous work up gave N4-(3-hydroxymethylen-4-methoxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine as a white solid. LCMS: purity: 89.2%; MS (m/e): 410.5 (MH⁺).

7.3.1155 N4-(3-Amino-4-ethoxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R950388)

A mixture of 2-chloro-N4-(3-amino-4-ethoxyphenyl)-5-fluoro-4-aminopyridine and 3 equivalents of 3-(N-methylamino)carbonylmethyleneoxyaniline in MeOH in a pressure tube at 110°C for 24h or in EtOH using microwave at 175°C for 10-20 min followed by aqueous work up gave N4-(3-amino-4-ethoxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine as a white solid. LCMS: purity: 95.1%; MS (m/e): 427.18 (MH⁺).

7.3.1156 N4-(4-Ethoxy-3-hydroxysulfonylphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R950389)

A solution of N4-(4-hydroxy-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine in HOAc was

treated with sodium nitrate followed by addition of concentrated aqueous HCl and copper dichloride. The mixture was stirred for 2 hours at 22°C for 8 hours and purified by aqueous work up followed by column chromatography on silica gel to give N4-(4-ethoxy-3-hydroxysulfonylphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. LCMS: purity: 82.3%; MS (m/e): 474.09 (M-H).

7.3.1157 N2,N4-Bis(3-methoxycarbonyl-4-trifluoromethoxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R950391)

A mixture of 2,4-dichloro-5-fluoropyridine and three equivalents of 3-methoxycarbonyl-4-trifluoromethoxyaniline in MeOH in a pressure tube at 110°C for 24h or in EtOH using microwave at 175°C for 10-20 min followed by aqueous work up N2,N4-bis(3-methoxycarbonyl-4-trifluoromethoxyphenyl)-5-fluoro-2,4-pyrimidinediamine as a white solid. ¹H NMR (DMSO): δ 9.96 (s, 1H), 9.82 (s, 1H), 8.16-8.26 (m, 4H), 7.91 (dd, 1H, J = 3.0, 7.2 Hz), 7.42 (d, 1H, J = 7.2 Hz), 7.31 (d, 1H, J = 7.2 Hz), 3.77 (s, 3H), 3.75 (s, 3H); LCMS: purity: 93.0%; MS (m/e): 565.37 (MH⁺).

7.3.1158 N4-(3-Methoxycarbonyl-4-trifluoromethoxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R950392)

A mixture of equimolar amounts of 2-chloro-N4-(3-methoxycarbonyl-4-trifluoromethoxyphenyl)-5-fluoro-4-aminopyridine and 3-(N-methylamino)carbonylmethyleneoxyaniline in MeOH in a pressure tube at 110°C for 24h or in EtOH using microwave at 175°C for 10-20 min followed by aqueous work up gave N4-(3-methoxycarbonyl-4-trifluoromethoxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine as a white solid. LCMS: purity: 95.8%; MS (m/e): 510.41 (MH⁺).

7.3.1159 N4-(4-Acetylamino-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R950393)

A solution of N4-(4-hydroxy-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine in dry MeCN was treated with concentrated sulfuric acid. The mixture was stirred for 3 hours at 22°C, concentrated to dryness and purified by flash chromatography on silica gel to give N4-(4-acetylamino-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine as a white solid. ¹H

NMR (DMSO): δ 10.46 (bs, 1H), 9.52 (bs, 1H), 7.98 (d, 1H, $J = 2.4$ Hz), 7.12-7.73 (m, 7H), 6.66 (d, 1H, $J = 7.2$ Hz), 6.49 (d, 1H, $J = 7.2$ Hz), 4.75 (s, 2H), 4.03-4.32 (m, 2H), 3.80 (m, 1H), 2.64 (s, 3H), 2.143 (s, 3H), 1.90-2.11 (m, 2H); LCMS: purity: 92.1%; MS (m/e): 393.06 (M-H). LCMS: purity: 96.2%; MS (m/e): 479.13 (M-H).

5 **7.3.1160 N4-(4-Amino-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethylene oxyphenyl]-2,4-pyrimidinediamine HCl salt (R950399)**

10 A solution of N4-(4-amino-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine in MeOH was treated with 1 equivalent of 1 N aqueous HCl. The clear solution was concentrated to dryness and the remaining solid was washed with dry acetone to give the HCl salt of N4-(4-amino-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine as a white solid. LCMS: purity: 98.2%; MS (m/e): 438.98 (MH⁺).

15 **7.3.1161 N4-(4-Amino-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethylene oxyphenyl]-2,4-pyrimidinediamine succinic acid salt (R950400)**

20 A solution of N4-(4-amino-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine in MeOH was treated with 1 equivalent of succinic acid. The clear solution was concentrated to dryness and the remaining solid was crystallized from dry acetone to give the succinic acid salt of N4-(4-amino-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine as a white solid. LCMS: purity: 98.1%; MS (m/e): 438.98 (MH⁺).

25 **7.3.1162 N4-(4-Amino-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethylene oxyphenyl]-2,4-pyrimidinediamine maleic acid salt (R950401)**

30 A solution of N4-(4-amino-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine in MeOH was treated with 1 equivalent of maleic acid. The clear solution was concentrated to dryness and the remaining solid was crystallized from dry acetone to give the maleic acid salt of N4-(4-amino-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-(N-

methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine as a white solid. LCMS: purity: 97.9%; MS (m/e): 438.98 (MH⁺).

7.3.1163 N4-(4-Amino-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine fumaric acid salt (R950402)

A solution of N4-(4-amino-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine in MeOH was treated with 1 equivalent of fumaric acid. The clear solution was concentrated to dryness and the remaining solid was crystallized from dry acetone to give the fumaric acid salt of N4-(4-amino-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine as a white solid. LCMS: purity: 97.9%; MS (m/e): 438.98 (MH⁺).

7.3.1164 N4-(4-Amino-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine citric acid salt (R950403)

A solution of N4-(4-amino-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine in MeOH was treated with 1 equivalent of citric acid. The clear solution was concentrated to dryness and the remaining solid was crystallized from dry acetone to give the citric acid salt of N4-(4-amino-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine as a white solid. LCMS: purity: 97.9%; MS (m/e): 438.98 (MH⁺).

7.3.1165 N4-(4-Amino-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine HNO₃ salt (R950404)

A solution of N4-(4-amino-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine in MeOH was treated with 1 equivalent of 1 N aqueous HNO₃. The clear solution was concentrated to dryness and the remaining solid was washed with dry acetone to give the nitric acid salt of N4-(4-amino-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine as a white solid. LCMS: purity: 98.2%; MS (m/e): 438.98 (MH⁺).

7.4 Synthesis of Prodrugs

Exemplary prodrugs according to structural formula (II) were synthesized as described below.

7.4.1 N-2(4)-Acetyl-N2,N4-bis(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R926233)

A mixture of N2,N4-bis(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine, acetyl chloride (4 equivalents), pyridine (4 equivalents) in CH₂Cl₂ was stirred at room temperature for 48h. After an aqueous work up the residue was chromatographed on silica gel to give N-2(4)-acetyl-N2,N4-bis(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine. ¹H NMR (CDCl₃): δ 8.23 (d, 1H, J= 5.4 Hz), 7.03 (d, 1H, J= 2.4 Hz), 7.90-7.80 (m, 3H), 6.76 (m, 2H), 4.28 (bs, 4H), 2.10 (s, 3H); ¹⁹F NMR (CDCl₃): -42125; LCMS: ret. time: 27.94 min.; purity: 99%; MS (m/e): 439 (MH⁺).

7.4.2 N2,N4-Bis(3-N-acetylaminophenyl)-5-fluoro-N2,N4-pyrimidinediacetylamine (R950244)

N2,N4-Bis(3-aminophenyl)-5-fluoro-2,4-pyrimidinediamine, dimethylaminopyridine (DMAP) and acetic anhydride were refluxed in pyridine for 1 hour. The mixture was cooled to room temperature, concentrated, and the residue was subjected to column chromatography on silica gel (CHCl₃:Acetone, 2:1) to give N2,N4-bis(3-N-acetylaminophenyl)-5-fluoro-N2,N4-pyrimidinediacetylamine. LCMS: ret. time: 17.03 min.; purity: 87.0%; MS (m/e): 478.89 (MH⁺).

7.4.3 N4-(3-N,N-Diacetylaminophenyl)-N2-(3-N-acetylaminophenyl)-5-fluoro-N2,N4-pyrimidinediacetylamine (R950245)

N2,N4-Bis(3-aminophenyl)-5-fluoro-2,4-pyrimidinediamine, dimethylaminopyridine (DMAP) and acetic anhydride were refluxed in pyridine for 1 hour. The mixture was cooled to room temperature, concentrated, and the residue was subjected to column chromatography on silica gel (CHCl₃:Acetone, 2:1) to give N4-(3-N,N-diacetylaminophenyl)-N2-(3-N-acetylaminophenyl)-5-fluoro-N2,N4-pyrimidinediacetylamine. LCMS: ret. time: 19.27 min.; purity: 92.6%; MS (m/e): 521.01 (MH⁺).

7.4.4 N4-(3-N-Acetylaminophenyl)-N2-(3-N,N-diacetylaminophenyl)-5-fluoro-N2,N4-pyrimidinediacetylamine (R950246)

N2,N4-Bis(3-aminophenyl)-5-fluoro-2,4-pyrimidinediamine,
5 dimethylaminopyridine (DMAP) and acetic anhydride were refluxed in pyridine for 1 hour. The mixture was cooled to room temperature, concentrated, and the residue was subjected to column chromatography on silica gel (CHCl₃:Acetone, 2:1) to give N4-[3-N-acetylaminophenyl]-N2-(3-N,N-diacetylaminophenyl)-5-fluoro-N2,N4-pyrimidinediacetylamine. LCMS: ret. time: 18.89 min.; purity: 83.0%; MS (m/e): 520.97
10 (MH⁺).

7.4.5 N2,N4-Bis(3-N,N-diacetylaminophenyl)-5-fluoro-N2,N4-pyrimidinediacetylamine (R950247)

N2,N4-Bis(3-aminophenyl)-5-fluoro-2,4-pyrimidinediamine,
dimethylaminopyridine (DMAP) and acetic anhydride were refluxed in pyridine for 1 hour.
15 The mixture was cooled to room temperature, concentrated, and the residue was subjected to column chromatography on silica gel (CHCl₃:Acetone, 2:1) to give N2,N4-bis(3-N,N-diacetylaminophenyl)-5-fluoro-N2,N4-pyrimidinediacetylamine. LCMS: ret. time: 21.51 min.; purity: 91.8%; MS (m/e): 563.00 (MH⁺).

7.5 The 2,4-Pyrimidinediamine Compounds of the Invention Inhibit FcεRI Receptor-Mediated Degranulation

The ability of the 2,4-pyrimidinediamine compounds of the invention to inhibit IgE-induced degranulation was demonstrated in a variety of cellular assays with cultured human mast cells (CHMC) and/or mouse bone marrow derived cells (BMMC). Inhibition of
25 degranulation was measured at both low and high cell density by quantifying the release of the granule specific factors tryptase, histamine and hexosaminidase. Inhibition of release and/or synthesis of lipid mediators was assessed by measuring the release of leukotriene LTC₄ and inhibition of release and/or synthesis of cytokines was monitored by quantifying TNF-α, IL-6 and IL-13. Tryptase and hexosaminidase were quantified using fluorogenic
30 substrates as described in their respective examples. Histamine, TNFα, IL-6, IL-13 and LTC₄ were quantified using the following commercial ELISA kits: histamine (Immunotech #2015, Beckman Coulter), TNFα (Biosource #KHC3011), IL-6 (Biosource #KMC0061),

IL-13 (Biosource #KHC0132) and LTC4 (Cayman Chemical #520211). The protocols of the various assays are provided below.

7.5.1 Culturing of Human Mast and Basophil Cells

Human mast and basophil cells were cultured from CD34-negative progenitor cells as described below (see also the methods described in copending U.S. application Serial No. 10/053,355, filed November 8, 2001, the disclosure of which is incorporated herein by reference).

7.5.1.1 Preparation of STEMPRO-34 Complete Medium

To prepare STEMPRO-34 complete medium ("CM"), 250 mL STEMPRO-34™ serum free medium ("SFM"; GibcoBRL, Catalog No. 10640) was added to a filter flask. To this was added 13 mL STEMPRO-34 Nutrient Supplement ("NS"; GibcoBRL, Catalog No. 10641) (prepared as described in more detail, below). The NS container was rinsed with approximately 10 mL SFM and the rinse added to the filter flask. Following addition of 5 mL L-glutamine (200 mM; Mediatech, Catalog No. MT 25-005-CI and 5 mL 100X penicillin/streptomycin ("pen-strep"; HyClone, Catalog No. SV30010), the volume was brought to 500 mL with SFM and the solution was filtered.

The most variable aspect of preparing the CM is the method by which the NS is thawed and mixed prior to addition to the SFM. The NS should be thawed in a 37° C water bath and swirled, not vortexed or shaken, until it is completely in solution. While swirling, take note whether there are any lipids that are not yet in solution. If lipids are present and the NS is not uniform in appearance, return it to the water bath and repeat the swirling process until it is uniform in appearance. Sometimes this component goes into solution immediately, sometimes after a couple of swirling cycles, and sometimes not at all. If, after a couple of hours, the NS is still not in solution, discard it and thaw a fresh unit. NS that appears non-uniform after thaw should not be used.

7.5.1.2 Expansion of CD34+ Cells

A starting population of CD34-positive (CD34+) cells of relatively small number ($1-5 \times 10^6$ cells) was expanded to a relatively large number of CD34-negative progenitor cells (about $2-4 \times 10^9$ cells) using the culture media and methods described below. The CD34+ cells (from a single donor) were obtained from Allcells (Berkeley, CA). Because there is a degree of variation in the quality and number of CD34+ cells that Allcells

typically provides, the newly delivered cells were transferred to a 15 mL conical tube and brought up to 10 mL in CM prior to use.

On day 0, a cell count was performed on the viable (phase-bright) cells and the cells were spun at 1200 rpm to pellet. The cells were resuspended to a density of 275,000 cells/mL with CM containing 200 ng/mL recombinant human Stem Cell Factor ("SCF"; Peprotech, Catalog No. 300-07) and 20 ng/mL human flt-3 ligand (Peprotech, Catalog No. 300-19) ("CM/SCF/flt-3 medium"). On about day 4 or 5, the density of the culture was checked by performing a cell count and the culture was diluted to a density of 275,000 cells/mL with fresh CM/SCF/flt-3 medium. On about day 7, the culture was transferred to a sterile tube and a cell count was performed. The cells were spun at 1200 rpm and resuspended to a density of 275,000 cells/mL with fresh CM/SCF/flt-3 medium.

This cycle was repeated, starting from day 0, a total of 3-5 times over the expansion period.

When the culture is large and being maintained in multiple flasks and is to be resuspended, the contents of all of the flasks are combined into a single container prior to performing a cell count. This ensures that an accurate cell count is achieved and provides for a degree of uniformity of treatment for the entire population. Each flask is checked separately for contamination under the microscope prior to combining to prevent contamination of the entire population.

Between days 17-24, the culture can begin to go into decline (*i.e.*, approximately 5-10% of the total number of cells die) and fail to expand as rapidly as before. The cells are then monitored on a daily basis during this time, as complete failure of the culture can take place in as little as 24 hours. Once the decline has begun, the cells are counted, spun down at 850 rpm for 15 minutes, and resuspended at a density of 350,000 cells/mL in CM/SCF/flt-3 medium to induce one or two more divisions out of the culture. The cells are monitored daily to avoid failure of the culture.

When greater than 15% cell death is evident in the progenitor cell culture and some debris is present in the culture, the CD34-negative progenitor cells are ready to be differentiated.

7.5.1.3 Differentiation of CD34-Negative Progenitor Cells into Mucosal Mast Cells

A second phase is performed to convert the expanded CD34-negative progenitor cells into differentiated mucosal mast cells. These mucosal cultured human mast

cells ("CHMC") are derived from CD34+ cells isolated from umbilical cord blood and treated to form a proliferated population of CD34-negative progenitor cells, as described above. To produce the CD43-negative progenitor cells, the resuspension cycle for the culture was the same as that described above, except that the culture was seeded at a density of 425,000 cells/mL and 15% additional media was added on about day four or five without performing a cell count. Also, the cytokine composition of the medium was modified such that it contained SCF (200 ng/mL) and recombinant human IL-6 (200 ng/mL; Peprotech, Catalog No. 200-06 reconstituted to 100 ug/mL in sterile 10 mM acetic acid) ("CM/SCF/IL-6 medium").

Phases I and II together span approximately 5 weeks. Some death and debris in the culture is evident during weeks 1-3 and there is a period during weeks 2-5 during which a small percentage of the culture is no longer in suspension, but is instead attached to the surface of the culture vessel.

As during Phase I, when the culture is to be resuspended on day seven of each cycle, the contents of all flasks are combined into a single container prior to performing a cell count to ensure uniformity of the entire population. Each flask is checked separately for contamination under the microscope prior to combining to prevent contamination of the entire population.

When the flasks are combined, approximately 75% of the volume is transferred to the communal container, leaving behind about 10 mL or so in the flask. The flask containing the remaining volume was rapped sharply and laterally to dislodge the attached cells. The rapping was repeated at a right angle to the first rap to completely dislodge the cells.

The flask was leaned at a 45 degree angle for a couple of minutes before the remaining volume was transferred to the counting vessel. The cells were spun at 950 rpm for 15 min prior to seeding at 35-50 mL per flask (at a density of 425,000 cells/mL).

7.5.1.4 Differentiation of CD34-Negative Progenitor Cells into Connective Tissue-Type Mast Cells

A proliferated population of CD34-negative progenitor cells is prepared as above and treated to form a tryptase/chymase positive (connective tissue) phenotype. The methods are performed as described above for mucosal mast cells, but with the substitution of IL-4 for IL-6 in the culture medium. The cells obtained are typical of connective tissue mast cells.

7.5.1.5 Differentiation of CD34-Negative Progenitor Cells into Basophil Cells

A proliferated population of CD34-negative progenitor cells is prepared as described in Section 6.4.1.2, above, and used to form a proliferated population of basophil cells. The CD34-negative cells are treated as described for mucosal mast cells, but with the substitution of IL-3 (at 20-50 ng/mL) for IL-6 in the culture medium.

7.5.2 CHMC Low Cell Density IgE Activation: Tryptase and LTC₄ Assays

To duplicate 96-well U-bottom plates (Costar 3799) add 65 ul of compound dilutions or control samples that have been prepared in MT [137 mM NaCl, 2.7 mM KCl, 1.8 mM CaCl₂, 1.0 mM MgCl₂, 5.6 mM Glucose, 20 mM Hepes (pH 7.4), 0.1% Bovine Serum Albumin, (Sigma A4503)] containing 2% MeOH and 1% DMSO. Pellet CHMC cells (980 rpm, 10 min) and resuspend in pre-warmed MT. Add 65 ul of cells to each 96-well plate. Depending on the degranulation activity for each particular CHMC donor, load 1000-1500 cells/well. Mix four times followed by a 1 hr incubation at 37°C. During the 1 hr incubation, prepare 6X anti-IgE solution [rabbit anti-human IgE (1 mg/ml, Bethyl Laboratories A80-109A) diluted 1:167 in MT buffer]. Stimulate cells by adding 25 ul of 6X anti-IgE solution to the appropriate plates. Add 25 ul MT to un-stimulated control wells. Mix twice following addition of the anti-IgE. Incubate at 37°C for 30 minutes. During the 30 minute incubation, dilute the 20 mM tryptase substrate stock solution [(Z-Ala-Lys-Arg-AMC·2TFA; Enzyme Systems Products, #AMC-246)] 1:2000 in tryptase assay buffer [0.1 M Hepes (pH 7.5), 10 % w/v Glycerol, 10 uM Heparin (Sigma H-4898) 0.01% NaN₃]. Spin plates at 1000 rpm for 10 min to pellet cells. Transfer 25 ul of supernatant to a 96-well black bottom plate and add 100 ul of freshly diluted tryptase substrate solution to each well. Incubate plates at room temperature for 30 min. Read the optical density of the plates at 355nm/460nm on a spectrophotometric plate reader.

Leukotriene C₄ (LTC₄) is also quantified using an ELISA kit on appropriately diluted supernatant samples (determined empirically for each donor cell population so that the sample measurement falls within the standard curve) following the supplier's instructions.

7.5.3 CHMC High Cell Density IgE Activation: Degranulation (Tryptase, Histamine), Leukotriene (LTC₄), and Cytokine (TNF α , IL-13) Assays

Cultured human mast cells (CHMC) are sensitized for 5 days with IL-4 (20 ng/ml), SCF (200 ng/ml), IL-6 (200 ng/ml), and Human IgE (CP 1035K from Cortex Biochem, 100-500ng/ml depending on generation) in CM medium. After sensitizing, cells are counted, pelleted (1000 rpm, 5-10 minutes), and resuspended at $1-2 \times 10^6$ cells/ml in MT buffer. Add 100 μ l of cell suspension to each well and 100 μ l of compound dilutions. The final vehicle concentration is 0.5% DMSO. Incubate at 37°C (5% CO₂) for 1 hour. After 1 hour of compound treatment, stimulate cells with 6X anti-IgE. Mix wells with the cells and allow plates to incubate at 37°C (5% CO₂) for one hour. After 1 hour incubation, pellet cells (10 minutes, 1000 RPM) and collect 200 μ l per well of the supernatant, being careful not to disturb pellet. Place the supernatant plate on ice. During the 7-hour step (see next) perform tryptase assay on supernatant that had been diluted 1:500. Resuspend cell pellet in 240 μ l of CM media containing 0.5% DMSO and corresponding concentration of compound. Incubate CHMC cells for 7 hours at 37°C (5% CO₂). After incubation, pellet cells (1000 RPM, 10 minutes) and collect 225 μ l per well and place in -80°C until ready to perform ELISAS. ELISAS are performed on appropriately diluted samples (determined empirically for each donor cell population so that the sample measurement falls within the standard curve) following the supplier's instructions.

7.5.4 BMMC High Cell Density IgE Activation: Degranulation (Hexosaminidase, Histamine), Leukotriene (LTC₄), and Cytokine (TNF α , IL-6) Assays

7.5.4.1 Preparation of WEHI-Conditioned Medium

WEHI-conditioned medium was obtained by growing murine myelomonocytic WEHI-3B cells (American Type Culture Collection, Rockville, MD) in Iscove's Modified Eagles Media (Mediatech, Herndon, VA) supplemented with 10% heat-inactivated fetal bovine serum (FBS; JRH Biosciences, Kansas City, MO), 50 μ M 2-mercaptoethanol (Sigma, St. Louis, MO) and 100 IU/mL penicillin-streptomycin (Mediatech) in a humidified 37°C, 5% CO₂/95% air incubator. An initial cell suspension was seeded at 200,000 cells/mL and then split 1:4 every 3-4 days over a period of two weeks. Cell-free supernatants were harvested, aliquoted and stored at -80°C until needed.

7.5.4.2 Preparation of BMMC Medium

BMMC media consists of 20% WEHI-conditioned media, 10% heat-inactivated FBS (JHR Biosciences), 25 mM HEPES, pH7.4 (Sigma), 2mM L-glutamine (Mediatech), 0.1 mM non-essential amino acids (Mediatech), 1mM sodium pyruvate (Mediatech), 50 μ M 2-mercaptoethanol (Sigma) and 100 IU/mL penicillin-streptomycin (Mediatech) in RPMI 1640 media (Mediatech). To prepare the BMMC Media, all components are added to a sterile IL filter unit and filtered through a 0.2 μ m filter prior to use.

7.5.4.3 Protocol

Bone marrow derived mast cells (BMMC) are sensitized overnight with murine SCF (20 ng/ml) and monoclonal anti-DNP (10 ng/ml, Clone SPE-7, Sigma # D-8406) in BMMC media at a cell density of 666×10^3 cells/ml. After sensitizing, cells are counted, pelleted (1000 rpm, 5-10 minutes), and resuspended at $1-3 \times 10^6$ cells/ml in MT buffer. Add 100 μ l of cell suspension to each well and 100 μ l of compound dilutions. The final vehicle concentration is 0.5% DMSO. Incubate at 37°C (5% CO₂) for 1 hour. After 1 hour of compound treatment, stimulate cells with 6X stimulus (60 ng/ml DNP-BSA). Mix wells with the cells and allow plates to incubate at 37°C (5% CO₂) for one hour. After 1 hour incubation, pellet cells (10 minutes, 1000 RPM) and collect 200 μ l per well of the supernatant, being careful not to disturb pellet, and transfer to a clean tube or 96-well plate. Place the supernatant plate on ice. During the 4-5 hour step (see next) perform the hexosiminidase assay. Resuspend cell pellet in 240 μ l WEI-conditioned media containing 0.5% DMSO and corresponding concentration of compound. Incubate BMMC cells for 4-5 hours at 37°C (5% CO₂). After incubation, pellet cells (1000 RPM, 10 minutes) and collect 225 μ l per well and place in -80°C until ready to perform ELISAS. ELISAS are performed on appropriately diluted samples (determined empirically for each donor cell population so that the sample measurement falls within the standard curve) following the supplier's instructions.

Hexosaminidase assay: In a solid black 96-well assay plate, add 50 μ L hexosaminidase substrate (4-methylumbelliferyl-N-acetyl- β -D-glucosaminide; 2mM) to each well. Add 50 μ L of BMMC cell supernatant (see above) to the hexoseaminidase substrate, place at 37°C for 30 minutes and read the plate at 5, 10, 15, and 30 minutes on a spectrophotometer.

7.5.5 Basophil IgE or Dustmite Activation: Histamine Release Assay

The basophil activation assay was carried out using whole human peripheral blood from donors allergic to dust mites with the majority of the red blood cells removed by dextran sedimentation. Human peripheral blood was mixed 1:1 with 3% dextran T500 and RBCs were allowed to settle for 20-25min. The upper fraction was diluted with 3 volumes of D-PBS and cells were spun down for 10 min at 1500 rpm, RT. Supernatant was aspirated and cells were washed in an equal volume MT-buffer. Finally, cells were resuspended in MT-buffer containing 0.5% DMSO in the original blood volume. 80 uL cells were mixed with 20 uL compound in the presence of 0.5% DMSO, in triplicate, in a V-bottom 96-well tissue culture plate. A dose range of 8 compound concentrations was tested resulting in a 10-point dose response curve including maximum (stimulated) and minimum (unstimulated) response. Cells were incubated with compound for 1 hour at 37°C, 5% CO₂ after which 20 uL of 6x stimulus [1 ug/mL anti-IgE (Bethyl Laboratories) 667 au/mL house dustmite (Antigen Laboratories)] was added. The cells were stimulated for 30 minutes at 37°C, 5% CO₂. The plate was spun for 10 min at 1500 rpm at room temperature and 80 uL the supernatant was harvested for histamine content analysis using the histamine ELISA kit supplied by Immunotech. The ELISA was performed according to supplier's instructions.

7.5.6 Results

The results of low density CHMC assays (Section 6.4.3), the high density BMCMC assays (Section 6.4.5) and the basophil assays (Section 6.4.6) are provided in TABLE 1. The results of the high density CHMC assays (Section 6.4.4) are provided in TABLE 2. In TABLES 1 and 2, all reported values are IC₅₀s (in μM). A value of "9999" indicates an IC₅₀ > 10 μM, with no measurable activity at a 10 μM concentration. Most compounds tested had IC₅₀s of less than 10 μM, with many exhibiting IC₅₀s in the sub-micromolar range.

7.6 The 2,4-Pyrimidinediamine Compounds Inhibit FcγRI Receptor-Mediated Degranulation

The ability of the 2,4-pyrimidinediamine compounds of the invention to inhibit FcγRI-mediated degranulation was demonstrated with Compounds R921218, R921302, R921303, R940347, R920410, R927050, R940350, R935372, R920323, R926971 and

R940352 in assays similar to those described in Section 6.4, with the exception that the cells were not primed with IgE and were activated with rabbit anti-human IgG Fab fragment (Bethyl Laboratories, Catalog No. A80-105).

All of the compounds tested exhibited IC_{50} s in the sub micromolar range.

TABLE 1

| Test Compound | Low Density | | | CHMC anti-IgE Tryptase | CHMC ionomycin Tryptase | CHMC anti-IgE LTC4 | CHMC anti-IgE Hexos. | CHMC ionomycin Hexos. | Basophils anti-IgE Histamine | Basophils ionomycin Histamine | Basophils Dust mite Histamine | High Density | | | | | |
|------------------|------------------------------|-------------------------------|--------------------------|------------------------------|-------------------------------|--------------------------|----------------------------|-----------------------------|------------------------------------|-------------------------------------|-------------------------------------|---------------------------|-----------------------------|-------------------------------|--------------------------|-------------------------------|--------------------------|
| | CHMC anti-IgE Tryptase | CHMC ionomycin Tryptase | CHMC anti-IgE LTC4 | | | | | | | | | BMMC anti-IgE hexos | BMMC ionomycin Hexos. | BMMC anti-IgE histamine | BMMC anti-IgE LTC4 | BMMC anti-IgE TNF-alpha | BMMC anti-IgE IL-6 |
| R008951 | | | | | | | | | | | | | | | | | |
| R008952 | | | | | | | | | | | | | | | | | |
| R008953 | | | | | | | | | | | | | | | | | |
| R008955 | | | | | | | | | | | | | | | | | |
| R008956 | | | | | | | | | | | | | | | | | |
| R008958 | | | | | | | | | | | | | | | | | |
| R067934 | | | | | | | | | | | | | | | | | |
| R067963 | | | | | | | | | | | | | | | | | |
| R070153 | | | | | | | | | | | | | | | | | |
| R070790 | 1.665 | 9999 | | | | | | | | | | | | | | | |
| R070791 | | | | | | | | | | | | | | | | | |
| R081166 | | | | | | | | | | | | | | | | | |
| R088814 | | | | | | | | | | | | | | | | | |
| R088815 | | | | | | | | | | | | | | | | | |
| R091880 | | | | | | | | | | | | | | | | | |
| R092788 | | | | | | | | | | | | | | | | | |
| R908696 | 3.553 | | | | | | | | | | | | | | | | |
| R908697 | 9999 | 9999 | | | | | | | | | | | | | | | |
| R909236 | 0.996 | 9999 | | | | | | | | | | | | | | | |
| R909237 | 9999 | 9999 | | | | | | | | | | | | | | | |
| R909238 | 0.174 | 9999 | | | | | | | | | | <0.22 | | <0.22 | 0.521 | 0.432 | <0.22 |
| R909239 | 0.264 | 9999 | | | | | | | | | | | | | | | |
| R909240 | 0.262 | 9999 | | | | | | | | | | | | | | | |

TABLE 1

| TABLE 1 | | | | | | | | | | | | | | | | |
|------------------|------------------------------|-------------------------------|--------------------------|---------------------------|----------------------------|-----------------------------|------------------------------------|-------------------------------------|-------------------------------------|-----------------------------|-------------------------------|--------------------------|-------------------------------|--------------------------|--|--|
| Test Compound | Low Density | | | | CHMC anti-IgE Hexos. | CHMC ionomycin Hexos. | Basophils anti-IgE Histamine | Basophils ionomycin Histamine | Basophils Dust mite Histamine | High Density | | | | | | |
| | CHMC anti-IgE Tryptase | CHMC ionomycin Tryptase | CHMC anti-IgE LTC4 | BMMC anti-IgE hexos | | | | | | BMMC ionomycin Hexos. | BMMC anti-IgE histamine | BMMC anti-IgE LTC4 | BMMC anti-IgE TNF-alpha | BMMC anti-IgE IL-6 | | |
| | | | | | | | | | | | | | | | | |
| R909241 | 0.181 | 9999 | | | | | | | | <0.22 | <0.22 | 1.021 | 0.253 | <0.22 | | |
| R909242 | 0.567 | 9999 | | | | | | | | | | | | | | |
| R909243 | 0.263 | >10 | | | | | | | | | | | | | | |
| R909245 | 0.255 | 6.242 | | | | | | | | | | | | | | |
| R909246 | 0.169 | 9999 | | | | | | | | | | | | | | |
| R909247 | 2.393 | 9999 | | | | | | | | | | | | | | |
| R909248 | 3.582 | 9999 | | | | | | | | | | | | | | |
| R909249 | 9999 | 9999 | | | | | | | | | | | | | | |
| R909250 | 8.025 | 9999 | | | | | | | | | | | | | | |
| R909251 | 0.138 | 9999 | | | | | | | | | | | | | | |
| R909252 | 0.248 | 9999 | | | | | | | | | | | | | | |
| R909253 | 7.955 | 9999 | | | | | | | | | | | | | | |
| R909254 | 0.136 | 9999 | | | | | | | | | | | | | | |
| R920664 | 9999 | 9999 | | | | | | | | | | | | | | |
| R920665 | 1.1 | 9999 | | | | | | | | | | | | | | |
| R920666 | 2.53 | 9999 | | | | | | | | | | | | | | |
| R920668 | 3.2 | 9999 | | | | | | | | | | | | | | |
| R920669 | 0.42 | 9999 | | | | | | | | | | | | | | |
| R920670 | 2.18 | 9999 | | | | | | | | | | | | | | |
| R920671 | 9999 | 9999 | | | | | | | | | | | | | | |
| R920672 | 9999 | 9999 | | | | | | | | | | | | | | |
| R920818 | 9999 | 9999 | | | | | | | | | | | | | | |
| R920819 | 10 | 9999 | | | | | | | | | | | | | | |

TABLE 1

| Test Compound | Low Density | | | CHMC anti-IgE Hexos. | CHMC Ionomycin Hexos. | Basophils anti-IgE Histamine | Basophils Ionomycin Histamine | Basophils Dust mite Histamine | High Density | | | | | |
|---------------|------------------------|-------------------------|--------------------|----------------------|-----------------------|------------------------------|-------------------------------|-------------------------------|---------------------|-----------------------|-------------------------|--------------------|-------------------------|--------------------|
| | CHMC anti-IgE Tryptase | CHMC Ionomycin Tryptase | CHMC anti-IgE LTC4 | | | | | | BMMC anti-IgE hexos | BMMC Ionomycin Hexos. | BMMC anti-IgE histamine | BMMC anti-IgE LTC4 | BMMC anti-IgE TNF-alpha | BMMC anti-IgE IL-6 |
| R920820 | 9999 | 9999 | | | | | | | | | | | | |
| R920846 | 9999 | 9999 | | | | | | | | | | | | |
| R920860 | 1.009 | 9999 | | | | | | | | | | | | |
| R920861 | 0.598 | >10 | | | | | | | | | | | | |
| R920893 | 1.239 | 9999 | | | | | | | | | | | | |
| R920894 | 0.888 | 5.566 | | | | | | | | | | | | |
| R920910 | 0.751 | 7.922 | | | | | | | | | | | | |
| R920917 | 1.579 | 9.729 | | | | | | | | | | | | |
| R921218 | 0.499 | 9999 | 0.55 | 0.6 | 9999 | 0.24 | 9999 | 0.302 | 0.133 | 9999 | 0.203 | 0.766 | 0.274 | 0.100 |
| R921219 | 0.059 | 9999 | | | | 0.025 | 9999 | 0.020 | 0.069 | | 0.058 | 0.040 | 0.039 | 0.009 |
| R925734 | | | | 9.2 | >10 | | | | 9999 | 9999 | | | | |
| R925747 | 1.021 | 3.1 | | | | | | | 3.1 | | | | | |
| R925755 | 0.898 | 9999 | | | | | | | | | | | | |
| R925757 | 2.8 | 9999 | | | | | | | | | | | | |
| R925758 | 1.175 | 9999 | | | | | | | | | | | | |
| R925760 | 4.85 | 9999 | | | | | | | | | | | | |
| R925765 | 6.8 | 9999 | | | | | | | | | | | | |
| R925766 | 8.9 | 9999 | | | | | | | | | | | | |
| R925767 | 10 | | | | | | | | | | | | | |
| R925768 | 9999 | | | | | | | | | | | | | |
| R925769 | 9999 | | | | | | | | | | | | | |
| R925770 | 9999 | | | | | | | | | | | | | |
| R925771 | 0.5 | 2.8 | 0.22 | | | | | | | | | | | |

TABLE 1

| TABLE 1 | | | | | | | | | | | | | | | | | |
|------------------|------------------------------|-------------------------------|--------------------------|---------------------------|----------------------------|-----------------------------|------------------------------------|-------------------------------------|-------------------------------------|-----------------------------|-------------------------------|--------------------------|-------------------------------|--------------------------|--|--|--|
| Test Compound | Low Density | | | | CHMC anti-IgE Hexos. | CHMC ionomycin Hexos. | Basophils anti-IgE Histamine | Basophils ionomycin Histamine | Basophils Dust mite Histamine | High Density | | | | | | | |
| | CHMC anti-IgE Tryptase | CHMC ionomycin Tryptase | CHMC anti-IgE LTC4 | BMMC anti-IgE hexos | | | | | | BMMC ionomycin Hexos. | BMMC anti-IgE histamine | BMMC anti-IgE LTC4 | BMMC anti-IgE TNF-alpha | BMMC anti-IgE IL-6 | | | |
| | | | | | | | | | | | | | | | | | |
| R925772 | 9999 | 9999 | | | | | | | | | | | | | | | |
| R925773 | 0.673 | 9999 | | | | | | | | | | | | | | | |
| R925774 | 0.435 | 9999 | | | | | | | | | | | | | | | |
| R925775 | 0.225 | 9999 | 0.2 | | | | | | | | | | | | | | |
| R925776 | 2.1 | 9999 | | | | | | | | | | | | | | | |
| R925778 | 0.225 | 9999 | 0.18 | | | | | | | | | | | | | | |
| R925779 | 0.265 | 9999 | 0.19 | | | | | | | | | | | | | | |
| R925783 | 2.9 | 9999 | | | | | | | | | | | | | | | |
| R925784 | 3.2 | 9999 | | | | | | | | | | | | | | | |
| R925785 | 2.5 | 9999 | | | | | | | | | | | | | | | |
| R925786 | 1.85 | 9999 | | | | | | | | | | | | | | | |
| R925787 | 9 | 9999 | | | | | | | | | | | | | | | |
| R925788 | 2.4 | 9999 | | | | | | | | | | | | | | | |
| R925790 | 9999 | 9999 | | | | | | | | | | | | | | | |
| R925791 | 9999 | 9999 | | | | | | | | | | | | | | | |
| R925792 | 6.25 | 9999 | | | | | | | | | | | | | | | |
| R925794 | 9999 | 9999 | | | | | | | | | | | | | | | |
| R925795 | 9999 | 9999 | | | | | | | | | | | | | | | |
| R925796 | 2 | 9999 | | | | | | | | | | | | | | | |
| R925797 | 0.85 | 9999 | 0.28 | | | | | | | | | | | | | | |
| R925798 | 9999 | 9999 | | | | | | | | | | | | | | | |
| R925799 | 9999 | 9999 | | | | | | | | | | | | | | | |
| R925800 | 9999 | 9999 | | | | | | | | | | | | | | | |

TABLE 1

| Test Compound | Low Density | | | CHMC anti-IgE Hexos. | CHMC anti-IgE Hexos. | CHMC Ionomycin Hexos. | Basophils anti-IgE Histamine | Basophils Ionomycin Histamine | Basophils Dust mite Histamine | High Density | | | | | |
|------------------|------------------------------|-------------------------------|--------------------------|----------------------------|----------------------------|-----------------------------|------------------------------------|-------------------------------------|-------------------------------------|---------------------------|-----------------------------|-------------------------------|--------------------------|-------------------------------|--------------------------|
| | CHMC anti-IgE Tryptase | CHMC Ionomycin Tryptase | CHMC anti-IgE LTC4 | | | | | | | BMHC anti-IgE hexos | BMHC Ionomycin Hexos. | BMHC anti-IgE histamine | BMHC anti-IgE LTC4 | BMHC anti-IgE TNF-alpha | BMHC anti-IgE IL-6 |
| R925801 | 9999 | 9999 | | | | | | | | | | | | | |
| R925802 | 9999 | 9999 | | | | | | | | | | | | | |
| R925803 | 9999 | 9999 | | | | | | | | | | | | | |
| R925804 | 9999 | 9999 | | | | | | | | | | | | | |
| R925805 | 9999 | 9999 | | | | | | | | | | | | | |
| R925806 | 9999 | 9999 | | | | | | | | | | | | | |
| R925807 | 9999 | 9999 | | | | | | | | | | | | | |
| R925808 | 9999 | 9999 | | | | | | | | | | | | | |
| R925810 | 9999 | 9999 | | | | | | | | | | | | | |
| R925811 | 3.3 | 9999 | | | | | | | | | | | | | |
| R925812 | 5.8 | 9999 | | | | | | | | | | | | | |
| R925813 | 9999 | 9999 | | | | | | | | | | | | | |
| R925814 | 9999 | 9999 | | | | | | | | | | | | | |
| R925815 | 9999 | 9999 | | | | | | | | | | | | | |
| R925816 | 6 | 9999 | | | | | | | | | | | | | |
| R925819 | 9999 | 9999 | | | | | | | | | | | | | |
| R925820 | 9999 | 9999 | | | | | | | | | | | | | |
| R925821 | 9999 | 9999 | | | | | | | | | | | | | |
| R925822 | 9999 | 9999 | | | | | | | | | | | | | |
| R925823 | 9999 | 9999 | | | | | | | | | | | | | |
| R925824 | 9999 | 9999 | | | | | | | | | | | | | |
| R925837 | 9999 | 9999 | | | | | | | | | | | | | |
| R925838 | 9999 | 9999 | | | | | | | | | | | | | |

TABLE 1

| TABLE 1 | | | | | | | | | | | | | | | | |
|------------------|------------------------------|-------------------------------|--------------------------|---------------------------|----------------------------|-----------------------------|------------------------------------|-------------------------------------|-------------------------------------|-----------------------------|-------------------------------|--------------------------|-------------------------------|--------------------------|--|--|
| Test Compound | Low Density | | | | CHMC anti-IgE Hexos. | CHMC Ionomycin Hexos. | Basophils anti-IgE Histamine | Basophils Ionomycin Histamine | Basophils Dust mite Histamine | High Density | | | | | | |
| | CHMC anti-IgE Tryptase | CHMC Ionomycin Tryptase | CHMC anti-IgE LTC4 | BMMC anti-IgE hexos | | | | | | BMMC Ionomycin Hexos. | BMMC anti-IgE histamine | BMMC anti-IgE LTC4 | BMMC anti-IgE TNF-alpha | BMMC anti-IgE IL-6 | | |
| | | | | | | | | | | | | | | | | |
| R925839 | 9999 | 9999 | | | | | | | | | | | | | | |
| R925840 | 9999 | 9999 | | | | | | | | | | | | | | |
| R925841 | 9999 | 9999 | | | | | | | | | | | | | | |
| R925842 | 7.3 | 9999 | | | | | | | | | | | | | | |
| R925843 | 9999 | 9999 | | | | | | | | | | | | | | |
| R925844 | 5.1 | 9999 | | | | | | | | | | | | | | |
| R925845 | 2.3 | 9999 | | | | | | | | | | | | | | |
| R925846 | 9999 | 9999 | | | | | | | | | | | | | | |
| R925849 | 8.2 | 9999 | | | | | | | | | | | | | | |
| R925851 | 0.925 | 9999 | | | | | | | | | | | | | | |
| R925852 | 3 | 9999 | | | | | | | | | | | | | | |
| R925853 | 9999 | 9999 | | | | | | | | | | | | | | |
| R925854 | 9999 | 9999 | | | | | | | | | | | | | | |
| R925855 | 4.2 | 9999 | | | | | | | | | | | | | | |
| R925856 | 9.85 | 9999 | | | | | | | | | | | | | | |
| R925857 | 5.95 | 9999 | | | | | | | | | | | | | | |
| R925858 | 8.05 | 7.3 | | | | | | | | | | | | | | |
| R925859 | 9999 | 9999 | | | | | | | | | | | | | | |
| R925860 | 9999 | 9999 | | | | | | | | | | | | | | |
| R925861 | 9999 | 9999 | | | | | | | | | | | | | | |
| R925862 | 0.7 | 9999 | | | | | | | | | | | | | | |
| R925863 | 0.274 | 9999 | | | | | | | | | | | | | | |
| R925864 | 9999 | 9999 | | | | | | | | | | | | | | |

TABLE 1

| Test Compound | Low Density | | | CHMC anti-IgE Hexos. | CHMC Ionomycin Hexos. | Basophils anti-IgE Histamine | Basophils Ionomycin Histamine | Basophils Dust mite Histamine | High Density | | | | | |
|---------------|------------------------|-------------------------|--------------------|----------------------|-----------------------|------------------------------|-------------------------------|-------------------------------|----------------------|-----------------------|-------------------------|--------------------|-------------------------|--------------------|
| | CHMC anti-IgE Tryptase | CHMC Ionomycin Tryptase | CHMC anti-IgE LTC4 | | | | | | BMMC anti-IgE hexos. | BMMC Ionomycin Hexos. | BMMC anti-IgE histamine | BMMC anti-IgE LTC4 | BMMC anti-IgE TNF-alpha | BMMC anti-IgE IL-6 |
| R925865 | 9999 | 9999 | | | | | | | | | | | | |
| R926016 | | | | | | 9999 | 9999 | | 9999 | 9999 | | | | |
| R926017 | | | | 1.43 | 9999 | 0.53 | 9999 | | 1.4 | 9.6 | | | | |
| R926018 | | | | | | 9999 | 10 | | 8.5 | 9999 | | | | |
| R926037 | | | | | | 9999 | 9999 | | 9999 | 9999 | | | | |
| R926038 | | | | | | 9999 | 9999 | | 9999 | 9999 | | | | |
| R926039 | | | | | | 9999 | 9999 | | 9999 | 9999 | | | | |
| R926058 | | | | | | 9999 | 9999 | | 9999 | 9999 | | | | |
| R926064 | | | | 6.2 | | | | | 5.9 | 7.3 | | | | |
| R926065 | | | | 3.5 | | | | | 9999 | 9999 | | | | |
| R926068 | | | | >10 | | | | | 7.4 | 8.2 | | | | |
| R926069 | | | | 9.1 | | | | | 4.5 | 4.4 | | | | |
| R926072 | | | | >10 | | | | | 9999 | 9999 | | | | |
| R926086 | | | | | | 2.5 | 9999 | | 2.8 | 7.3 | | | | |
| R926108 | | | 0.76 | 0.787 | 6.4 | 0.95 | 9999 | | 0.9 | 9999 | | | | |
| R926109 | 0.538 | 5.5 | 0.73 | 0.55 | >10 | 0.15 | 9999 | | 0.6 | 3.2 | | | | |
| R926110 | 1.071 | 9999 | 1.42 | 1.2 | >10 | 0.3 | 9999 | | 1 | 4.5 | | | | |
| R926113 | 0.413 | | 0.49 | 0.413 | 9999 | 0.27 | 9999 | | 0.65 | 9999 | | | | |
| R926114 | | | | 3.427 | 8.1 | 1.7 | 10 | | 9999 | 9999 | | | | |
| R926145 | | | | 4.764 | >10 | | | | 2.4 | 8.8 | | | | |
| R926146 | | | 1.59 | 0.761 | 6.7 | | | | 1.35 | 5 | | | | |
| R926147 | | | | 1.899 | >10 | | | | 2 | 7.1 | | | | |
| R926206 | | | | | | >10 | >10 | | 6.6 | 8.6 | | | | |

TABLE 1

| TABLE 1 | | | | | | | | | | | | | | | | |
|------------------|------------------------------|-------------------------------|--------------------------|---------------------------|----------------------------|-----------------------------|------------------------------------|-------------------------------------|-------------------------------------|-----------------------------|-------------------------------|--------------------------|-------------------------------|--------------------------|--|--|
| Test Compound | Low Density | | | | CHMC anti-IgE Hexos. | CHMC Ionomycin Hexos. | Basophils anti-IgE Histamine | Basophils Ionomycin Histamine | Basophils Dust mite Histamine | High Density | | | | | | |
| | CHMC anti-IgE Tryptase | CHMC Ionomycin Tryptase | CHMC anti-IgE LTC4 | BMMC anti-IgE hexos | | | | | | BMMC Ionomycin Hexos. | BMMC anti-IgE histamine | BMMC anti-IgE LTC4 | BMMC anti-IgE TNF-alpha | BMMC anti-IgE IL-6 | | |
| | | | | | | | | | | | | | | | | |
| R926209 | | | | | | | >10 | 9999 | | | 10 | 9.1 | | | | |
| R926210 | 0.926 | 9999 | 0.8 | 700 | 9999 | | 0.37 | >10 | | | 0.6 | >10 | | | | |
| R926211 | 1.299 | 9.8 | | 2.7 | 9999 | | 1.55 | >10 | | | 3.9 | >10 | | | | |
| R926212 | 0.654 | 9999 | 0.45 | | | | 0.5 | >10 | | | 0.5 | 5 | | | | |
| R926213 | 1.639 | 5.5 | | | | | 1.75 | >10 | | | | | | | | |
| R926218 | | | | >10 | | | | | | | 9999 | 9999 | | | | |
| R926219 | | | | 1.102 | 6.7 | | | | | | 2.5 | 3.2 | | | | |
| R926220 | | | | >10 | | | | | | | 9999 | 9999 | | | | |
| R926221 | | | | 8.5 | | | | | | | 9.9 | 9999 | | | | |
| R926222 | | | | >10 | | | | | | | 9999 | 9999 | | | | |
| R926223 | | | | >10 | | | | | | | 9999 | 9999 | | | | |
| R926224 | | | | >10 | | | | | | | 9999 | 9999 | | | | |
| R926225 | | | | >10 | | | | | | | 9999 | 9999 | | | | |
| R926228 | | | | >10 | | | | | | | 9999 | | | | | |
| R926229 | | | | >10 | | | | | | | | | | | | |
| R926230 | | | | >10 | | | | | | | | | | | | |
| R926234 | | | | >10 | | | | | | | 9999 | | | | | |
| R926237 | 1.207 | 6.2 | | | | | | | | | 1.9 | | | | | |
| R926240 | 0.381 | 1.7 | 0.145 | | | | | | | | | | | | | |
| R926241 | 7 | 9999 | | | | | | | | | | | | | | |
| R926242 | 4.2 | 9999 | | | | | | | | | | | | | | |
| R926243 | 3.1 | 9999 | | | | | | | | | | | | | | |
| R926245 | 3.1 | 9.4 | | | | | | | | | | | | | | |

TABLE 1

| TABLE 1 | | | | | | | | | | | | | | | | |
|---------------|------------------------|-------------------------|--------------------|----------------------|-----------------------|------------------------------|-------------------------------|-------------------------------|---------------------|-----------------------|-------------------------|--------------------|-------------------------|--------------------|--|--|
| Test Compound | Low Density | | | CHMC anti-IgE Hexos. | CHMC Ionomycin Hexos. | Basophils anti-IgE Histamine | Basophils Ionomycin Histamine | Basophils Dust mite Histamine | High Density | | | | | | | |
| | CHMC anti-IgE Tryptase | CHMC Ionomycin Tryptase | CHMC anti-IgE LTC4 | | | | | | BMMC anti-IgE hexos | BMMC Ionomycin Hexos. | BMMC anti-IgE histamine | BMMC anti-IgE LTC4 | BMMC anti-IgE TNF-alpha | BMMC anti-IgE IL-6 | | |
| R926248 | 0.9 | 9999 | 0.76 | | | | | | | | | | | | | |
| R926249 | 0.5 | 9999 | 0.25 | | | | | | | | | | | | | |
| R926252 | 2.8 | | | | | | | | | | | | | | | |
| R926253 | 0.8 | | 0.675 | | | | | | | | | | | | | |
| R926254 | 1.3 | 4 | | | | | | | | | | | | | | |
| R926255 | 1.4 | 4.5 | | | | | | | | | | | | | | |
| R926256 | 0.275 | 5.1 | 0.23 | | | | | | | | | | | | | |
| R926257 | 1.5 | 7.5 | | | | | | | | | | | | | | |
| R926258 | 0.9 | 9999 | 0.59 | | | | | | | | | | | | | |
| R926259 | 2.5 | 6.2 | | | | | | | | | | | | | | |
| R926319 | 9999 | 9999 | | | | | | | | | | | | | | |
| R926320 | 9999 | 9999 | | | | | | | | | | | | | | |
| R926321 | 9999 | 9999 | | | | | | | | | | | | | | |
| R926325 | 9999 | 9999 | | | | | | | | | | | | | | |
| R926331 | 9999 | 9999 | | | | | | | | | | | | | | |
| R926339 | 0.66 | 9999 | | | | | | | | | | | | | | |
| R926340 | 3.23 | 9999 | | | | | | | | | | | | | | |
| R926341 | 0.875 | 9999 | | | | | | | | | | | | | | |
| R926342 | 10 | 9999 | | | | | | | | | | | | | | |
| R926376 | 9999 | | | | | | | | | | | | | | | |
| R926386 | 9999 | 9999 | | | | | | | | | | | | | | |
| R926387 | 0.65 | 9999 | 0.7 | | | | | | | | | | | | | |
| R926394 | 9999 | 9999 | | | | | | | | | | | | | | |

TABLE 1

| Test Compound | Low Density | | | CHMC anti-IgE Hexos. | CHMC ionomycin Hexos. | Basophils anti-IgE Histamine | Basophils ionomycin Histamine | Basophils Dust mite Histamine | High Density | | | | | |
|------------------|------------------------------|-------------------------------|--------------------------|----------------------------|-----------------------------|------------------------------------|-------------------------------------|-------------------------------------|---------------------------|-----------------------------|-------------------------------|--------------------------|-------------------------------|--------------------------|
| | CHMC anti-IgE Tryptase | CHMC ionomycin Tryptase | CHMC anti-IgE LTC4 | | | | | | CHMC anti-IgE hexos | CHMC ionomycin Hexos. | CHMC anti-IgE histamine | CHMC anti-IgE LTC4 | CHMC anti-IgE TNF-alpha | CHMC anti-IgE IL-6 |
| R926395 | 0.875 | 6.4 | 0.29 | | | | | | | | | | | |
| R926396 | 0.7 | 2.6 | 0.16 | | | | | | | | | | | |
| R926397 | 9999 | 9999 | | | | | | | | | | | | |
| R926398 | 9999 | 9999 | | | | | | | | | | | | |
| R926399 | 9999 | 9999 | | | | | | | | | | | | |
| R926400 | 9999 | 9999 | | | | | | | | | | | | |
| R926401 | 9999 | 9999 | | | | | | | | | | | | |
| R926402 | 9999 | 9999 | | | | | | | | | | | | |
| R926403 | 9999 | 9999 | | | | | | | | | | | | |
| R926404 | 9999 | 9999 | | | | | | | | | | | | |
| R926405 | 3.4 | 9999 | | | | | | | | | | | | |
| R926406 | 9999 | 9999 | | | | | | | | | | | | |
| R926408 | 9.6 | 9999 | | | | | | | | | | | | |
| R926409 | 3.15 | 9999 | | | | | | | | | | | | |
| R926411 | 0.69 | 2.5 | | | | | | | | | | | | |
| R926412 | 0.62 | 9999 | | | | | | | | | | | | |
| R926461 | 0.725 | 9999 | | | | | | | | | | | | |
| R926467 | 1.175 | 8.8 | | | | | | | | | | | | |
| R926469 | 9999 | | | | | | | | | | | | | |
| R926474 | 2.5 | 9999 | | | | | | | | | | | | |
| R926475 | 2.15 | >10 | | | | | | | | | | | | |
| R926476 | 0.6 | 7.7 | | | | | | | | | | | | |
| R926477 | 0.27 | 9999 | | | | | | | | | | | | |

TABLE 1

| TABLE 1 | | | | | | | | | | | | | | | | |
|------------------|------------------------------|-------------------------------|--------------------------|----------------------------|-----------------------------|------------------------------------|-------------------------------------|-------------------------------------|---------------------------|-----------------------------|-------------------------------|--------------------------|-------------------------------|--------------------------|--|--|
| Test Compound | Low Density | | | CHMC anti-IgE Hexos. | CHMC ionomycin Hexos. | Basophils anti-IgE Histamine | Basophils ionomycin Histamine | Basophils Dust mite Histamine | High Density | | | | | | | |
| | CHMC anti-IgE Tryptase | CHMC ionomycin Tryptase | CHMC anti-IgE LTC4 | | | | | | BMMC anti-IgE hexos | BMMC ionomycin Hexos. | BMMC anti-IgE histamine | BMMC anti-IgE LTC4 | BMMC anti-IgE TNF-alpha | BMMC anti-IgE IL-6 | | |
| R926478 | 9999 | | | | | | | | | | | | | | | |
| R926479 | 9999 | | | | | | | | | | | | | | | |
| R926480 | 1.9 | 9999 | | | | | | | | | | | | | | |
| R926481 | 1.445 | 9999 | | | | | | | | | | | | | | |
| R926482 | 1.037 | >10 | | | | | | | | | | | | | | |
| R926483 | 9999 | | | | | | | | | | | | | | | |
| R926484 | 1.523 | 9999 | | | | | | | | | | | | | | |
| R926485 | 4.012 | 9999 | | | | | | | | | | | | | | |
| R926486 | 0.647 | 7.403 | | | | | | | | | | | | | | |
| R926487 | 0.554 | 8.867 | 1.25 | | | | | | | | | | | | | |
| R926488 | 0.331 | >10 | 0.752 | | | | | | | | | | | | | |
| R926489 | 1.414 | >10 | | | | | | | | | | | | | | |
| R926490 | 1.571 | 9999 | | | | | | | | | | | | | | |
| R926491 | 1.158 | >10 | | | | | | | | | | | | | | |
| R926492 | 0.645 | 9999 | | | | | | | | | | | | | | |
| R926493 | 0.25 | 9.181 | 0.078 | | | | | | | | | | | | | |
| R926494 | 0.313 | 9999 | 0.078 | | | | | | | | | | | | | |
| R926495 | 0.121 | >10 | 0.078 | | | 0.04 | 9999 | 0.038 | 0.056 | | 0.089 | 0.24 | 0.077 | 0.028 | | |
| R926496 | 0.571 | >10 | | | | | | | | | | | | | | |
| R926497 | 0.138 | 9999 | | | 0.27 | 9999 | 9999 | 0.205 | | | | | | | | |
| R926498 | 0.209 | >10 | | | | | | | <0.22 | | 0.515 | 0.995 | 0.614 | <0.22 | | |
| R926499 | 0.29 | >10 | | | | | | | | | | | | | | |
| R926500 | 0.418 | >10 | | | | | | | | | | | | | | |

TABLE 1

| TABLE 1 | | | | | | | | | | | | | | | | |
|---------------|------------------------|-------------------------|--------------------|---------------------|----------------------|-----------------------|------------------------------|-------------------------------|-------------------------------|-----------------------|-------------------------|--------------------|-------------------------|--------------------|--|--|
| Test Compound | Low Density | | | | CHMC anti-IgE Hexos. | CHMC Ionomycin Hexos. | Basophils anti-IgE Histamine | Basophils Ionomycin Histamine | Basophils Dust mite Histamine | High Density | | | | | | |
| | CHMC anti-IgE Tryptase | CHMC Ionomycin Tryptase | CHMC anti-IgE LTC4 | BMMC anti-IgE hexos | | | | | | BMMC Ionomycin Hexos. | BMMC anti-IgE histamine | BMMC anti-IgE LTC4 | BMMC anti-IgE TNF-alpha | BMMC anti-IgE IL-6 | | |
| | | | | | | | | | | | | | | | | |
| R926501 | 0.298 | >10 | | | | | 0.609 | 9999 | 0.645 | | | | | | | |
| R926502 | 0.483 | >10 | | | | | 0.405 | 9999 | 0.491 | | | | | | | |
| R926503 | 0.452 | >10 | | | | | | | | | | | | | | |
| R926504 | 0.569 | >10 | | | | | | | | | | | | | | |
| R926505 | 0.145 | 9999 | | | | | | | | | | | | | | |
| R926506 | 0.343 | 9999 | | | | | | | | | | | | | | |
| R926508 | 0.127 | 9999 | | | | | | | | | | | | | | |
| R926509 | 1.16 | 9999 | | | | | | | | | | | | | | |
| R926510 | 0.44 | >10 | | | | | | | | | | | | | | |
| R926511 | 0.786 | >10 | | | | | | | | | | | | | | |
| R926514 | 9999 | 9999 | | | | | | | | | | | | | | |
| R926516 | 1 | 9999 | | | | | | | | | | | | | | |
| R926526 | 9999 | 9999 | | | | | | | | | | | | | | |
| R926527 | 9999 | 9999 | | | | | | | | | | | | | | |
| R926528 | 8.75 | 9999 | | | | | | | | | | | | | | |
| R926535 | 9999 | 9999 | | | | | | | | | | | | | | |
| R926536 | 9999 | 9999 | | | | | | | | | | | | | | |
| R926555 | 9999 | 9999 | | | | | | | | | | | | | | |
| R926559 | 7.7 | 9999 | | | | | | | | | | | | | | |
| R926560 | 9999 | 9999 | | | | | | | | | | | | | | |
| R926562 | 9999 | 9999 | | | | | | | | | | | | | | |
| R926563 | 9999 | 9999 | | | | | | | | | | | | | | |
| R926564 | 3.75 | 9999 | | | | | | | | | | | | | | |

TABLE 1

| TABLE 1 | | | | | | | | | | | | | | | | |
|---------------|------------------------|-------------------------|--------------------|---------------------|----------------------|-----------------------|------------------------------|-------------------------------|-------------------------------|-----------------------|-------------------------|--------------------|-------------------------|--------------------|--|--|
| Test Compound | Low Density | | | | CHMC anti-IgE Hexos. | CHMC Ionomycin Hexos. | Basophils anti-IgE Histamine | Basophils Ionomycin Histamine | Basophils Dust mite Histamine | High Density | | | | | | |
| | CHMC anti-IgE Tryptase | CHMC Ionomycin Tryptase | CHMC anti-IgE LTC4 | BMMC anti-IgE hexos | | | | | | BMMC Ionomycin Hexos. | BMMC anti-IgE histamine | BMMC anti-IgE LTC4 | BMMC anti-IgE TNF-alpha | BMMC anti-IgE IL-6 | | |
| | | | | | | | | | | | | | | | | |
| R926565 | 0.625 | 3.3 | | | | | | | | | | | | | | |
| R926566 | 2.73 | 9999 | | | | | | | | | | | | | | |
| R926567 | 9.3 | 9999 | | | | | | | | | | | | | | |
| R926569 | 0.61 | 3.07 | | | | | | | | | | | | | | |
| R926571 | 9999 | 9999 | | | | | | | | | | | | | | |
| R926572 | 1.8 | 6.08 | | | | | | | | | | | | | | |
| R926574 | 1.96 | 2.63 | | | | | | | | | | | | | | |
| R926576 | 9999 | 9999 | | | | | | | | | | | | | | |
| R926579 | 9999 | 9999 | | | | | | | | | | | | | | |
| R926580 | 10 | 9999 | | | | | | | | | | | | | | |
| R926582 | 1.3 | 9999 | | | | | | | | | | | | | | |
| R926583 | 9999 | 9999 | | | | | | | | | | | | | | |
| R926584 | 9999 | 9999 | | | | | | | | | | | | | | |
| R926585 | 9999 | 9999 | | | | | | | | | | | | | | |
| R926586 | 2.75 | 9999 | | | | | | | | | | | | | | |
| R926587 | 9999 | 9999 | | | | | | | | | | | | | | |
| R926588 | 7.85 | 9999 | | | | | | | | | | | | | | |
| R926589 | 0.325 | 10 | | | | | | | | | | | | | | |
| R926591 | 2.62 | 9999 | | | | | | | | | | | | | | |
| R926593 | 0.68 | 8.3 | 0.495 | | | | | | | | | | | | | |
| R926594 | 9999 | 9999 | | | | | | | | | | | | | | |
| R926595 | 4.85 | 9999 | | | | | | | | | | | | | | |
| R926604 | 2.85 | 9999 | | | | | | | | | | | | | | |

TABLE 1

| TABLE 1 | | | | | | | | | | | | | | | | |
|------------------|------------------------------|-------------------------------|--------------------------|---------------------------|----------------------------|-----------------------------|------------------------------------|-------------------------------------|-------------------------------------|-----------------------------|-------------------------------|--------------------------|-------------------------------|--------------------------|--|--|
| Test Compound | Low Density | | | | CHMC anti-IgE Hexos. | CHMC Ionomycin Hexos. | Basophils anti-IgE Histamine | Basophils Ionomycin Histamine | Basophils Dust mite Histamine | High Density | | | | | | |
| | CHMC anti-IgE Tryptase | CHMC Ionomycin Tryptase | CHMC anti-IgE LTC4 | BMMC anti-IgE hexos | | | | | | BMMC Ionomycin Hexos. | BMMC anti-IgE histamine | BMMC anti-IgE LTC4 | BMMC anti-IgE TNF-alpha | BMMC anti-IgE IL-6 | | |
| | | | | | | | | | | | | | | | | |
| R926605 | 2.45 | 9999 | | | | | | | | | | | | | | |
| R926614 | 0.228 | 9999 | | | | | | | | | | | | | | |
| R926615 | 0.445 | 9999 | | | | | | | | | | | | | | |
| R926616 | 0.625 | 3.25 | | | | | | | | | | | | | | |
| R926617 | 9.45 | 9999 | | | | | | | | | | | | | | |
| R926620 | 8.35 | 9999 | | | | | | | | | | | | | | |
| R926623 | 9999 | 9999 | | | | | | | | | | | | | | |
| R926662 | 9999 | 9999 | | | | | | | | | | | | | | |
| R926663 | 9999 | 9999 | | | | | | | | | | | | | | |
| R926675 | 0.63 | 9999 | | | | | | | | | | | | | | |
| R926676 | 0.76 | 9999 | | | | | | | | | | | | | | |
| R926680 | 1.71 | 9999 | | | | | | | | | | | | | | |
| R926681 | 0.775 | 9999 | | | | | | | | | | | | | | |
| R926682 | 8.41 | 9999 | | | | | | | | | | | | | | |
| R926683 | 10 | 9999 | | | | | | | | | | | | | | |
| R926688 | 2.25 | >10 | | | | | | | | | | | | | | |
| R926690 | 0.146 | >10 | | | | | | | | | | | | | | |
| R926696 | 0.309 | >10 | | | | | | | | | | | | | | |
| R926698 | 9999 | | | | | | | | | | | | | | | |
| R926699 | 0.76 | 9999 | | | | | | | | | | | | | | |
| R926700 | 0.157 | >10 | | | | | | | | | | | | | | |
| R926701 | 2.2 | 9999 | | | | | | | | | | | | | | |
| R926702 | 0.886 | 9999 | | | | | | | | | | | | | | |

TABLE 1

| TABLE 1 | | | | | | | | | | | | | | | | |
|------------------|------------------------------|-------------------------------|--------------------------|---------------------------|----------------------------|-----------------------------|------------------------------------|-------------------------------------|-------------------------------------|-----------------------------|-------------------------------|--------------------------|-------------------------------|--------------------------|--|--|
| Test Compound | Low Density | | | | CHMC anti-IgE Hexos. | CHMC lonomycin Hexos. | Basophils anti-IgE Histamine | Basophils lonomycin Histamine | Basophils Dust mite Histamine | High Density | | | | | | |
| | CHMC anti-IgE Tryptase | CHMC lonomycin Tryptase | CHMC anti-IgE LTC4 | BMMC anti-IgE hexos | | | | | | BMMC lonomycin Hexos. | BMMC anti-IgE histamine | BMMC anti-IgE LTC4 | BMMC anti-IgE TNF-alpha | BMMC anti-IgE IL-6 | | |
| | | | | | | | | | | | | | | | | |
| R926703 | 0.525 | 9999 | | | | | | | | | | | | | | |
| R926704 | 0.564 | 9999 | | | | | | | | | | | | | | |
| R926705 | 0.263 | 9999 | 0.533 | | | | | | | | | | | | | |
| R926706 | 0.07 | 2.406 | 0.078 | | | | | | | | | | | | | |
| R926707 | 0.214 | 9999 | | | | | | | | | | | | | | |
| R926708 | 0.472 | 9999 | | | | | | | | | | | | | | |
| R926709 | 0.858 | 9999 | | | | | | | | | | | | | | |
| R926710 | 1.763 | 9999 | | | | | | | | | | | | | | |
| R926711 | 1.245 | 9999 | | | | | | | | | | | | | | |
| R926712 | 1.084 | 9999 | | | | | | | | | | | | | | |
| R926713 | 0.446 | 8.741 | | | | | | | | | | | | | | |
| R926714 | 0.428 | >10 | | | | | | | | | | | | | | |
| R926715 | 0.588 | >10 | | | | | | | | | | | | | | |
| R926716 | 1.06 | 9999 | | | | | | | | | | | | | | |
| R926717 | 7.874 | 9999 | | | | | | | | | | | | | | |
| R926718 | 1.826 | 9999 | | | | | | | | | | | | | | |
| R926719 | 0.1335 | 4.024 | | | | | | | | | | | | | | |
| R926720 | 1.555 | 9999 | | | | | | | | | | | | | | |
| R926721 | 4.441 | 9999 | | | | | | | | | | | | | | |
| R926722 | 5.96 | 9999 | | | | | | | | | | | | | | |
| R926723 | 2.591 | 9999 | | | | | | | | | | | | | | |
| R926724 | 2.059 | 9999 | | | | | | | | | | | | | | |
| R926725 | 0.431 | 9999 | | | | | | | | | | | | | | |

TABLE 1

| TABLE 1 | | | | | | | | | | | | | | | | |
|------------------|------------------------------|-------------------------------|--------------------------|---------------------------|----------------------------|-----------------------------|------------------------------------|-------------------------------------|-------------------------------------|-----------------------------|-------------------------------|--------------------------|-------------------------------|--------------------------|-------|--|
| Test Compound | Low Density | | | | CHMC anti-IgE Hexos. | CHMC Ionomycin Hexos. | Basophils anti-IgE Histamine | Basophils Ionomycin Histamine | Basophils Dust mite Histamine | High Density | | | | | | |
| | CHMC anti-IgE Tryptase | CHMC Ionomycin Tryptase | CHMC anti-IgE LTC4 | BMMC anti-IgE hexos | | | | | | BMMC Ionomycin Hexos. | BMMC anti-IgE histamine | BMMC anti-IgE LTC4 | BMMC anti-IgE TNF-alpha | BMMC anti-IgE IL-6 | | |
| | | | | | | | | | | | | | | | | |
| R926726 | 9999 | 9999 | | | | | | | | | | | | | | |
| R926727 | 0.387 | 9999 | | | | | | | | | | | | | | |
| R926728 | 0.482 | >10 | | | | | | | | | | | | | | |
| R926730 | 0.251 | 9999 | | | | | | | | | | | | | | |
| R926731 | 9999 | 9999 | | | | | | | | | | | | | | |
| R926732 | 0.444 | 9999 | | | | | | | | | | | | | | |
| R926733 | 1.496 | 9999 | | | | | | | | | | | | | | |
| R926734 | 4.493 | 9999 | | | | | | | | | | | | | | |
| R926735 | 3.712 | 9999 | | | | | | | | | | | | | | |
| R926736 | 0.288 | 9999 | | | | | | | | | | | | | | |
| R926737 | 0.059 | 9999 | | | | | | | | 0.075 | | 0.073 | 0.046 | 0.068 | 0.017 | |
| R926738 | 0.342 | 9999 | | | | | | | | | | | | | | |
| R926739 | 0.508 | 9999 | | | | | | | | | | | | | | |
| R926740 | 4.422 | 9999 | | | | | | | | | | | | | | |
| R926741 | 2.908 | 9999 | | | | | | | | 0.961 | | 1.025 | 9999 | 0.772 | 0.537 | |
| R926742 | 0.127 | | | | | | 0.043 | 9999 | 0.055 | 0.041 | | 0.055 | 0.105 | 0.053 | 0.022 | |
| R926743 | 9999 | | | | | | | | | | | | | | | |
| R926744 | 9999 | | | | | | | | | | | | | | | |
| R926745 | 0.083 | 9999 | | | | | | | | | | | | | | |
| R926746 | 0.989 | 9999 | | | | | | | | | | | | | | |
| R926747 | 0.213 | >10 | | | | | | | | | | | | | | |
| R926748 | 0.345 | >10 | | | | | | | | | | | | | | |
| R926749 | 0.472 | 9999 | | | | | | | | | | | | | | |

TABLE 1

| Test Compound | Low Density | | | CHMC anti-IgE Hexos. | CHMC Ionomycin Hexos. | Basophils anti-IgE Histamine | Basophils Ionomycin Histamine | Basophils Dust mite Histamine | High Density | | | | | | |
|------------------|------------------------------|-------------------------------|--------------------------|----------------------------|-----------------------------|------------------------------------|-------------------------------------|-------------------------------------|---------------------------|-----------------------------|-------------------------------|--------------------------|-------------------------------|--------------------------|-------|
| | CHMC anti-IgE Tryptase | CHMC Ionomycin Tryptase | CHMC anti-IgE LTC4 | | | | | | BMMC anti-IgE hexos | BMMC Ionomycin Hexos. | BMMC anti-IgE histamine | BMMC anti-IgE LTC4 | BMMC anti-IgE TNF-alpha | BMMC anti-IgE IL-6 | |
| | | | | | | | | | | | | | | | |
| R926750 | 0.361 | >10 | | | | | | | | | | | | | |
| R926751 | 0.598 | 9999 | | | | | | | | | | | | | |
| R926764 | 0.252 | 5.64 | | | | | | | | | | | | | |
| R926765 | 0.324 | 4.39 | | | | | | | | | | | | | |
| R926766 | 0.756 | 9999 | | | | | | | | | | | | | |
| R926767 | 0.387 | >10 | | | | | | | | | | | | | |
| R926768 | 0.443 | >10 | | | | | | | | | | | | | |
| R926769 | 1.067 | 9999 | | | | | | | | | | | | | |
| R926770 | 0.583 | 9999 | | | | | | | | | | | | | |
| R926771 | 2.049 | 9999 | | | | | | | | | | | | | |
| R926772 | 0.337 | 7.501 | | | | | | | | | | | | | |
| R926773 | 0.548 | 7.849 | | | | | | | | | | | | | |
| R926774 | 1.934 | 7.935 | | | | | | | | | | | | | |
| R926775 | 3.47 | >10 | | | | | | | | | | | | | |
| R926776 | 0.81 | 9999 | | | | | | | | | | | | | |
| R926777 | 0.378 | 9999 | | | | | | | | | | | | | |
| R926778 | 0.414 | 9999 | | | | | | | | | | | | | |
| R926779 | 9999 | 9999 | | | | | | | | | | | | | |
| R926780 | 0.152 | >10 | | | | | | | | <0.22 | <0.22 | 0.461 | <0.22 | <0.22 | <0.22 |
| R926781 | 0.573 | 9999 | | | | | | | | | | | | | |
| R926782 | 0.173 | >10 | | | | | | | | <0.22 | <0.22 | 1.461 | 0.276 | <0.22 | <0.22 |
| R926783 | 0.304 | >10 | | | | | | | | | | | | | |
| R926784 | 0.252 | 9999 | | | | | | | | | | | | | |

TABLE 1

| Test Compound | Low Density | | | CHMC anti-IgE Hexos. | CHMC anti-IgE Hexos. | CHMC Ionomycin Hexos. | Basophils anti-IgE Histamine | Basophils Ionomycin Histamine | Basophils Dust mite Histamine | High Density | | | | | |
|------------------|------------------------------|-------------------------------|--------------------------|----------------------------|----------------------------|-----------------------------|------------------------------------|-------------------------------------|-------------------------------------|---------------------------|-----------------------------|-------------------------------|--------------------------|-------------------------------|--------------------------|
| | CHMC anti-IgE Tryptase | CHMC Ionomycin Tryptase | CHMC anti-IgE LTC4 | | | | | | | BMMC anti-IgE hexos | BMMC Ionomycin Hexos. | BMMC anti-IgE histamine | BMMC anti-IgE LTC4 | BMMC anti-IgE TNF-alpha | BMMC anti-IgE IL-6 |
| R926785 | 0.222 | >10 | | | | | | | | 0.989 | | 0.561 | 1.411 | 1.312 | 0.513 |
| R926786 | 0.504 | 9999 | | | | | | | | | | | | | |
| R926787 | 5.422 | 9999 | | | | | | | | | | | | | |
| R926788 | 0.336 | 6.341 | | | | | | | | | | | | | |
| R926789 | 2.315 | 9999 | | | | | | | | | | | | | |
| R926790 | 0.462 | 7.412 | | | | | | | | | | | | | |
| R926791 | 0.233 | >10 | | | | | | | | 0.064 | | <0.056 | 0.896 | 0.205 | <0.056 |
| R926792 | 3.197 | 9999 | | | | | | | | | | | | | |
| R926793 | 3.073 | 9999 | | | | | | | | | | | | | |
| R926795 | 2.041 | >10 | | | | | | | | | | | | | |
| R926796 | 0.914 | 9999 | | | | | | | | | | | | | |
| R926797 | 2.235 | 9999 | | | | | | | | | | | | | |
| R926798 | 2.347 | 5.87 | | | | | | | | | | | | | |
| R926799 | 9999 | 9999 | | | | | | | | | | | | | |
| R926800 | 4.581 | 9999 | | | | | | | | | | | | | |
| R926801 | 10 | 9999 | | | | | | | | | | | | | |
| R926802 | 1.251 | >10 | | | | | | | | | | | | | |
| R926803 | 1.541 | >10 | | | | | | | | | | | | | |
| R926804 | 1.578 | 7.109 | | | | | | | | | | | | | |
| R926805 | 0.764 | 9999 | | | | | | | | | | | | | |
| R926806 | 0.374 | 9999 | | | | | | | | | | | | | |
| R926807 | 0.291 | 9999 | | | | | | | | | | | | | |
| R926808 | 0.368 | 9999 | | | | | | | | | | | | | |

TABLE 1

| TABLE 1 | | | | | | | | | | | | | | | | | |
|------------------|------------------------------|-------------------------------|--------------------------|---------------------------|----------------------------|-----------------------------|------------------------------------|-------------------------------------|-------------------------------------|-----------------------------|-------------------------------|--------------------------|-------------------------------|--------------------------|--|--|--|
| Test Compound | Low Density | | | | CHMC anti-IgE Hexos. | CHMC Ionomycin Hexos. | Basophils anti-IgE Histamine | Basophils Ionomycin Histamine | Basophils Dust mite Histamine | High Density | | | | | | | |
| | CHMC anti-IgE Tryptase | CHMC Ionomycin Tryptase | CHMC anti-IgE LTC4 | BMMC anti-IgE hexos | | | | | | BMMC Ionomycin Hexos. | BMMC anti-IgE histamine | BMMC anti-IgE LTC4 | BMMC anti-IgE TNF-alpha | BMMC anti-IgE IL-6 | | | |
| | | | | | | | | | | | | | | | | | |
| R926809 | 0.78 | 3.052 | | | | | | | | | | | | | | | |
| R926810 | 1.221 | 9999 | | | | | | | | | | | | | | | |
| R926811 | 3.662 | 9999 | | | | | | | | | | | | | | | |
| R926812 | 0.185 | >10 | | | | | | | | | | | | | | | |
| R926813 | 0.152 | 9999 | | | | | | | | | | | | | | | |
| R926814 | 1.101 | 9999 | | | | | | | | | | | | | | | |
| R926815 | 1.181 | 9999 | | | | | | | | | | | | | | | |
| R926816 | 0.084 | 9999 | | | | | | | | | | | | | | | |
| R935000 | 9999 | 9999 | | | | | | | | | | | | | | | |
| R935001 | 9999 | 9999 | | | | | | | | | | | | | | | |
| R935002 | 9999 | 9999 | | | | | | | | | | | | | | | |
| R935003 | 9999 | 9999 | | | | | | | | | | | | | | | |
| R935004 | 9999 | 9999 | | | | | | | | | | | | | | | |
| R935005 | 9999 | 9999 | | | | | | | | | | | | | | | |
| R935006 | 10 | 9.8 | | | | | | | | | | | | | | | |
| R935016 | 9999 | 9999 | | | | | | | | | | | | | | | |
| R935019 | 8.8 | 9999 | | | | | | | | | | | | | | | |
| R935020 | 9999 | 9999 | | | | | | | | | | | | | | | |
| R935021 | 9999 | 9999 | | | | | | | | | | | | | | | |
| R935023 | 9999 | 9999 | | | | | | | | | | | | | | | |
| R935025 | 1.04 | 9999 | | | | | | | | | | | | | | | |
| R935029 | 2.83 | 9999 | | | | | | | | | | | | | | | |
| R935075 | 0.93 | 9999 | | | | | | | | | | | | | | | |

TABLE 1

| Test Compound | Low Density | | | | CHMC anti-IgE Hexos. | CHMC ionomycin Hexos. | Basophils anti-IgE Histamine | Basophils ionomycin Histamine | Basophils Dust mite Histamine | High Density | | | | | | |
|------------------|------------------------------|-------------------------------|--------------------------|---------------------------|----------------------------|-----------------------------|------------------------------------|-------------------------------------|-------------------------------------|-----------------------------|-------------------------------|--------------------------|-------------------------------|--------------------------|--|-------|
| | CHMC anti-IgE Tryptase | CHMC ionomycin Tryptase | CHMC anti-IgE LTC4 | BMMC anti-IgE hexos | | | | | | BMMC ionomycin Hexos. | BMMC anti-IgE histamine | BMMC anti-IgE LTC4 | BMMC anti-IgE TNF-alpha | BMMC anti-IgE IL-6 | | |
| | | | | | | | | | | | | | | | | |
| R935076 | 4.15 | 9999 | | | | | | | | | | | | | | |
| R935077 | 9999 | 9999 | | | | | | | | | | | | | | |
| R935114 | 1.725 | 9999 | | | | | | | | | | | | | | |
| R935117 | 9999 | | | | | | | | | | | | | | | |
| R935134 | 0.909 | 1.799 | | | | | | | | | | | | | | |
| R935135 | 10 | 9999 | | | | | | | | | | | | | | |
| R935136 | 0.952 | 2.129 | | | | | | | | | | | | | | |
| R935137 | 10 | 9999 | | | | | | | | | | | | | | |
| R935138 | 0.096 | 0.552 | | | | | | | | <0.22 | | <0.22 | 0.373 | 0.409 | | <0.22 |
| R935139 | 0.846 | 9999 | | | | | | | | | | | | | | |
| R935140 | 0.275 | 0.959 | | | | | | | | | | | | | | |
| R935141 | 0.727 | >10 | | | | | | | | | | | | | | |
| R935142 | 0.873 | >10 | | | | | | | | | | | | | | |
| R935143 | 0.573 | >10 | | | | | | | | | | | | | | |
| R935144 | 0.63 | 9999 | | | | | | | | | | | | | | |
| R935145 | 0.548 | >10 | | | | | | | | | | | | | | |
| R935146 | 3.802 | 9999 | | | | | | | | | | | | | | |
| R935147 | 1.404 | 9999 | | | | | | | | | | | | | | |
| R935148 | 2.218 | 9.423 | | | | | | | | | | | | | | |
| R935149 | 0.708 | >10 | | | | | | | | | | | | | | |
| R935150 | 1.926 | 9.738 | | | | | | | | | | | | | | |
| R935151 | 0.479 | >10 | | | | | | | | | | | | | | |
| R935152 | 0.505 | 9.316 | | | | | | | | | | | | | | |

TABLE 1

| TABLE 1 | | | | | | | | | | | | | | | | |
|------------------|------------------------------|-------------------------------|--------------------------|---------------------------|----------------------------|-----------------------------|------------------------------------|-------------------------------------|-------------------------------------|-----------------------------|-------------------------------|--------------------------|-------------------------------|--------------------------|--|--|
| Test Compound | Low Density | | | | CHMC anti-IgE Hexos. | CHMC ionomycin Hexos. | Basophils anti-IgE Histamine | Basophils ionomycin Histamine | Basophils Dust mite Histamine | High Density | | | | | | |
| | CHMC anti-IgE Tryptase | CHMC ionomycin Tryptase | CHMC anti-IgE LTC4 | BMMC anti-IgE hexos | | | | | | BMMC ionomycin Hexos. | BMMC anti-IgE histamine | BMMC anti-IgE LTC4 | BMMC anti-IgE TNF-alpha | BMMC anti-IgE IL-6 | | |
| | | | | | | | | | | | | | | | | |
| R935153 | 0.238 | >10 | | | | | | | | | | | | | | |
| R935154 | 0.127 | >10 | | | | | | | | | 0.085 | 0.547 | 0.131 | 0.041 | | |
| R935155 | 0.401 | 9999 | | | | | | | | | | | | | | |
| R935156 | 0.149 | >10 | | | | | | | | | <0.22 | 0.433 | 0.22 | <0.22 | | |
| R935157 | 0.256 | 4.656 | | | | | | | | | | | | | | |
| R935158 | 0.551 | >10 | | | | | | | | | | | | | | |
| R935159 | 0.232 | 4.135 | | | | | | | | | | | | | | |
| R935160 | 0.202 | >10 | | | | | | | | | <0.22 | 0.876 | 0.484 | <0.22 | | |
| R935161 | 0.277 | 9999 | | | | | | | | | | | | | | |
| R935162 | 0.269 | >10 | | | | | | | | | | | | | | |
| R935163 | 9999 | 9999 | | | | | | | | | | | | | | |
| R935164 | 0.204 | 9999 | | | | | | | | | | | | | | |
| R935165 | 4.988 | 9999 | | | | | | | | | | | | | | |
| R935166 | 0.568 | 9999 | | | | | | | | | | | | | | |
| R935167 | 2.132 | >10 | | | | | | | | | | | | | | |
| R935168 | 0.488 | 9.484 | | | | | | | | | | | | | | |
| R935169 | 0.999 | 8.007 | | | | | | | | | | | | | | |
| R935170 | 0.673 | 9999 | | | | | | | | | | | | | | |
| R935171 | 0.536 | 9999 | | | | | | | | | | | | | | |
| R935172 | 1.385 | 6.808 | | | | | | | | | | | | | | |
| R935173 | 0.454 | >10 | | | | | | | | | | | | | | |
| R935174 | 1.384 | 9999 | | | | | | | | | | | | | | |
| R935175 | 0.885 | 9999 | | | | | | | | | | | | | | |

TABLE 1

| TABLE 1 | | | | | | | | | | | | | | | | |
|------------------|------------------------------|-------------------------------|--------------------------|---------------------------|----------------------------|-----------------------------|------------------------------------|-------------------------------------|-------------------------------------|-----------------------------|-------------------------------|--------------------------|-------------------------------|--------------------------|--|--|
| Test Compound | Low Density | | | | CHMC anti-IgE Hexos. | CHMC ionomycin Hexos. | Basophils anti-IgE Histamine | Basophils ionomycin Histamine | Basophils Dust mite Histamine | High Density | | | | | | |
| | CHMC anti-IgE Tryptase | CHMC ionomycin Tryptase | CHMC anti-IgE LTC4 | BMMC anti-IgE hexos | | | | | | BMMC ionomycin Hexos. | BMMC anti-IgE histamine | BMMC anti-IgE LTC4 | BMMC anti-IgE TNF-alpha | BMMC anti-IgE IL-6 | | |
| | | | | | | | | | | | | | | | | |
| R935176 | 1.169 | 9999 | | | | | | | | | | | | | | |
| R935177 | 0.889 | >10 | | | | | | | | | | | | | | |
| R935178 | 0.515 | 9999 | | | | | | | | | | | | | | |
| R935179 | 0.557 | 9999 | | | | | | | | | | | | | | |
| R935180 | 1.22 | 9999 | | | | | | | | | | | | | | |
| R935181 | 1.76 | 9999 | | | | | | | | | | | | | | |
| R935182 | 0.124 | 2.469 | | | | | | | | | | | | | | |
| R935183 | 0.729 | 9999 | | | | | | | | | | | | | | |
| R935184 | 0.605 | 9999 | | | | | | | | | | | | | | |
| R935185 | 0.351 | 6.642 | | | | | | | | | | | | | | |
| R935186 | 0.211 | 9999 | | | | | | | | | | | | | | |
| R935187 | 9.059 | >10 | | | | | | | | | | | | | | |
| R935188 | 0.239 | 9999 | | | | | | | | | | | | | | |
| R935189 | 0.619 | 9999 | | | | | | | | | | | | | | |
| R935190 | 0.156 | 9999 | | | | | | | | | | | | | | |
| R935191 | 0.151 | 9999 | | | | | | | | 0.068 | 0.043 | 0.213 | 0.071 | 0.027 | | |
| R935192 | 0.337 | 9999 | | | | | | | | | | | | | | |
| R935193 | 0.136 | 9999 | | | | | | | | 0.08 | 0.048 | 0.312 | 0.092 | 0.037 | | |
| R935194 | 0.11 | 9999 | | | | | | | | 0.125 | 0.054 | 0.493 | 0.118 | 0.034 | | |
| R935196 | 0.117 | 9999 | | | | | | | | | | | | | | |
| R935197 | 0.174 | >10 | | | | | | | | | | | | | | |
| R935198 | 0.126 | >10 | | | | | | | | | | | | | | |
| R935199 | 0.45 | >10 | | | | | | | | | | | | | | |

TABLE 1

| TABLE 1 | | | | | | | | | | | | | | | | |
|------------------|------------------------------|-------------------------------|--------------------------|---------------------------|----------------------------|-----------------------------|------------------------------------|-------------------------------------|-------------------------------------|-----------------------------|-------------------------------|--------------------------|-------------------------------|--------------------------|--|--|
| Test Compound | Low Density | | | | CHMC anti-IgE Hexos. | CHMC Ionomycin Hexos. | Basophils anti-IgE Histamine | Basophils Ionomycin Histamine | Basophils Dust mite Histamine | High Density | | | | | | |
| | CHMC anti-IgE Tryptase | CHMC Ionomycin Tryptase | CHMC anti-IgE LTC4 | BMMC anti-IgE hexos | | | | | | BMMC Ionomycin Hexos. | BMMC anti-IgE histamine | BMMC anti-IgE LTC4 | BMMC anti-IgE TNF-alpha | BMMC anti-IgE IL-6 | | |
| | | | | | | | | | | | | | | | | |
| R935202 | 0.181 | 9.765 | | | | | | | | | | | | | | |
| R935203 | 0.562 | >10 | | | | | | | | | | | | | | |
| R935204 | 0.554 | 9999 | | | | | | | | | | | | | | |
| R935205 | 2.959 | 9999 | | | | | | | | | | | | | | |
| R935206 | 4.711 | 9999 | | | | | | | | | | | | | | |
| R935207 | 9999 | 9999 | | | | | | | | | | | | | | |
| R935208 | 1.274 | 9999 | | | | | | | | | | | | | | |
| R935209 | 0.526 | 1.035 | | | | | | | | | | | | | | |
| R935211 | 1.238 | 9999 | | | | | | | | | | | | | | |
| R935212 | 1.427 | 9999 | | | | | | | | | | | | | | |
| R935213 | 0.619 | 10 | | | | | | | | | | | | | | |
| R935214 | 0.453 | 5.499 | | | | | | | | | | | | | | |
| R935218 | 4.712 | 9999 | | | | | | | | | | | | | | |
| R935219 | 5.409 | 9999 | | | | | | | | | | | | | | |
| R935220 | 3.789 | 9999 | | | | | | | | | | | | | | |
| R940089 | 9999 | 9999 | | | | | | | | | | | | | | |
| R940090 | 9999 | 9999 | | | | | | | | | | | | | | |
| R940095 | 9999 | 9999 | | | | | | | | | | | | | | |
| R940100 | 9999 | 9999 | | | | | | | | | | | | | | |
| R940215 | 0.845 | 9999 | | | | | | | | | | | | | | |
| R940216 | 0.2675 | 7.3 | | | | | | | | | | | | | | |
| R940217 | 9999 | 9999 | | | | | | | | | | | | | | |
| R940222 | 9999 | 9999 | | | | | | | | | | | | | | |

TABLE 1

| TABLE 1 | | | | | | | | | | | | | | | |
|---------------|------------------------|-------------------------|--------------------|---------------------|----------------------|-----------------------|------------------------------|-------------------------------|-------------------------------|-----------------------|-------------------------|--------------------|-------------------------|--------------------|--------|
| Test Compound | Low Density | | | | CHMC anti-IgE Hexos. | CHMC Ionomycin Hexos. | Basophils anti-IgE Histamine | Basophils Ionomycin Histamine | Basophils Dust mite Histamine | High Density | | | | | |
| | CHMC anti-IgE Tryptase | CHMC Ionomycin Tryptase | CHMC anti-IgE LTC4 | BMMC anti-IgE hexos | | | | | | BMMC Ionomycin Hexos. | BMMC anti-IgE histamine | BMMC anti-IgE LTC4 | BMMC anti-IgE TNF-alpha | BMMC anti-IgE IL-6 | |
| | | | | | | | | | | | | | | | |
| R940233 | 0.132 | >10 | | | | | | | | | | | | | |
| R940235 | 0.8 | >10 | | | | | | | | | | | | | |
| R940250 | | | | | | | | | | | | | | | |
| R940251 | | | | | | | | | | | | | | | |
| R940253 | 1.006 | >10 | | | | | | | | | | | | | |
| R940254 | 0.986 | 9999 | | | | | | | | | | | | | |
| R940255 | 1.033 | 9999 | | | | | | | | | | | | | |
| R940256 | 1.104 | 9999 | | | | | | | | | | | | | |
| R940257 | 0.667 | 9999 | | | | | | | | | | | | | |
| R940258 | 0.473 | 5.72 | | | | | | | | | | | | | |
| R940260 | 1.126 | 9999 | | | | | | | | | | | | | |
| R940261 | 9999 | 9999 | | | | | | | | | | | | | |
| R940262 | 9999 | 9999 | | | | | | | | | | | | | |
| R940263 | 9999 | 9999 | | | | | | | | | | | | | |
| R940264 | 10 | 9999 | | | | | | | | | | | | | |
| R940265 | 0.239 | >10 | | | | | | | | 0.981 | | 0.306 | 1.211 | 1.131 | 0.486 |
| R940266 | 9999 | 9999 | | | | | | | | | | | | | |
| R940267 | 3.151 | 9999 | | | | | | | | | | | | | |
| R940269 | 1.654 | 9999 | | | | | | | | | | | | | |
| R940270 | 2.144 | 8.739 | | | | | | | | | | | | | |
| R940271 | 0.401 | 6.821 | | | | | | | | | | | | | |
| R940275 | 0.862 | 9999 | | | | | | | | | | | | | |
| R940276 | 0.211 | 9999 | | | | | | | | 0.136 | | 0.073 | 0.332 | 0.251 | <0.056 |

TABLE 1

| TABLE 1 | | | | | | | | | | | | | | | |
|------------------|------------------------------|-------------------------------|--------------------------|---------------------------|----------------------------|-----------------------------|------------------------------------|-------------------------------------|-------------------------------------|-----------------------------|-------------------------------|--------------------------|-------------------------------|--------------------------|-------|
| Test Compound | Low Density | | | | CHMC anti-IgE Hexos. | CHMC ionomycin Hexos. | Basophils anti-IgE Histamine | Basophils ionomycin Histamine | Basophils Dust mite Histamine | High Density | | | | | |
| | CHMC anti-IgE Tryptase | CHMC ionomycin Tryptase | CHMC anti-IgE LTC4 | BMMC anti-IgE hexos | | | | | | BMMC ionomycin Hexos. | BMMC anti-IgE histamine | BMMC anti-IgE LTC4 | BMMC anti-IgE TNF-alpha | BMMC anti-IgE IL-6 | |
| | | | | | | | | | | | | | | | |
| R940277 | 0.141 | 9999 | | | | | | | | 0.279 | | 0.315 | 0.625 | 0.262 | 0.181 |
| R940280 | 6.999 | 9999 | | | | | | | | | | | | | |
| R940281 | 0.525 | 5.529 | | | | | | | | | | | | | |
| R940282 | 0.401 | 3.015 | | | | | | | | | | | | | |
| R940283 | 0.553 | 4.982 | | | | | | | | | | | | | |
| R940284 | 0.465 | 3.744 | | | | | | | | | | | | | |
| R940285 | 3.499 | 9999 | | | | | | | | | | | | | |
| R940286 | 0.337 | 7.082 | | | | | | | | | | | | | |
| R940287 | 0.288 | 7.684 | | | | | | | | | | | | | |
| R940288 | 0.208 | 9999 | | | | | | | | | | | | | |
| R940289 | 0.272 | 9999 | | | | | | | | | | | | | |
| R940290 | 0.116 | 9999 | | | | | | | | 0.255 | | 0.545 | 0.59 | 0.246 | 0.1 |
| R940291 | 0.396 | 9999 | | | | | | | | | | | | | |
| R940292 | 0.683 | 9999 | | | | | | | | | | | | | |
| R940293 | 9999 | 9999 | | | | | | | | | | | | | |
| R940294 | 1.366 | 9999 | | | | | | | | | | | | | |
| R940295 | 0.126 | 8.812 | | | | | | | | | | | | | |
| R940296 | 0.41 | >10 | | | | | | | | | | | | | |
| R940297 | 3.465 | 10 | | | | | | | | | | | | | |
| R945025 | 9999 | 9999 | | | | | | | | | | | | | |
| R945032 | 0.37 | 9999 | | | | | | | | | | | | | |
| R945033 | 9999 | 9999 | | | | | | | | | | | | | |
| R945034 | 1.85 | 9999 | | | | | | | | | | | | | |

TABLE 1

| TABLE 1 | | | | | | | | | | | | | | | | |
|------------------|------------------------------|-------------------------------|--------------------------|---------------------------|----------------------------|-----------------------------|------------------------------------|-------------------------------------|-------------------------------------|-----------------------------|-------------------------------|--------------------------|-------------------------------|--------------------------|--|--|
| Test Compound | Low Density | | | | CHMC anti-IgE Hexos. | CHMC Ionomycin Hexos. | Basophils anti-IgE Histamine | Basophils Ionomycin Histamine | Basophils Dust mite Histamine | High Density | | | | | | |
| | CHMC anti-IgE Tryptase | CHMC Ionomycin Tryptase | CHMC anti-IgE LTC4 | BMMC anti-IgE hexos | | | | | | BMMC Ionomycin Hexos. | BMMC anti-IgE histamine | BMMC anti-IgE LTC4 | BMMC anti-IgE TNF-alpha | BMMC anti-IgE IL-6 | | |
| | | | | | | | | | | | | | | | | |
| R945035 | 9999 | 9999 | | | | | | | | | | | | | | |
| R945036 | 9999 | 9999 | | | | | | | | | | | | | | |
| R945037 | 9999 | 9999 | | | | | | | | | | | | | | |
| R945038 | 9999 | 9999 | | | | | | | | | | | | | | |
| R945040 | 9999 | 9999 | | | | | | | | | | | | | | |
| R945041 | 9999 | 9999 | | | | | | | | | | | | | | |
| R945042 | 9999 | 9999 | | | | | | | | | | | | | | |
| R945043 | 9999 | 9999 | | | | | | | | | | | | | | |
| R945045 | 9999 | 9999 | | | | | | | | | | | | | | |
| R945046 | 0.82 | >10 | | | | | | | | | | | | | | |
| R945047 | 0.845 | 9999 | | | | | | | | | | | | | | |
| R945048 | 0.76 | 9999 | | | | | | | | | | | | | | |
| R945051 | 0.95 | >10 | | | | | | | | | | | | | | |
| R945052 | 0.425 | 2.48 | | | | | | | | | | | | | | |
| R945053 | 0.1185 | 1.48 | | | | | | | | | | | | | | |
| R945056 | 10 | 9999 | | | | | | | | | | | | | | |
| R945057 | 10 | 9999 | | | | | | | | | | | | | | |
| R945060 | 0.9375 | >10 | | | | | | | | | | | | | | |
| R945061 | 10 | 9999 | | | | | | | | | | | | | | |
| R945062 | 0.625 | >10 | | | | | | | | | | | | | | |
| R945063 | 1.55 | >10 | | | | | | | | | | | | | | |
| R945064 | 0.53 | >10 | | | | | | | | | | | | | | |
| R945065 | 1.425 | >10 | | | | | | | | | | | | | | |

TABLE 1

| Test Compound | Low Density | | | CHMC anti-IgE Hexos. | CHMC Ionomycin Hexos. | Basophils anti-IgE Histamine | Basophils Ionomycin Histamine | Basophils Dust mite Histamine | High Density | | | | | | |
|---------------|------------------------|-------------------------|--------------------|----------------------|-----------------------|------------------------------|-------------------------------|-------------------------------|---------------------|-----------------------|-------------------------|--------------------|-------------------------|--------------------|--|
| | CHMC anti-IgE Tryptase | CHMC Ionomycin Tryptase | CHMC anti-IgE LTC4 | | | | | | BMMC anti-IgE hexos | BMMC Ionomycin Hexos. | BMMC anti-IgE histamine | BMMC anti-IgE LTC4 | BMMC anti-IgE TNF-alpha | BMMC anti-IgE IL-6 | |
| | | | | | | | | | | | | | | | |
| R945066 | 5.2 | nd | | | | | | | | | | | | | |
| R945067 | 9999 | nd | | | | | | | | | | | | | |
| R945068 | 9999 | nd | | | | | | | | | | | | | |
| R945070 | 0.45 | >10 | | | | | | | | | | | | | |
| R945071 | 0.205 | >10 | | | | | | | | | | | | | |
| R945096 | 1.75 | >10 | | | | | | | | | | | | | |
| R945097 | 10 | 9999 | | | | | | | | | | | | | |
| R945109 | 1.025 | >10 | | | | | | | | | | | | | |
| R945110 | 0.602 | 9999 | | | | | | | | | | | | | |
| R945117 | 4.077 | 9999 | | | | | | | | | | | | | |
| R945118 | 0.668 | 9999 | | | | | | | | | | | | | |
| R945124 | 0.69 | 7.852 | | | | | | | | | | | | | |
| R945125 | 0.896 | >10 | | | | | | | | | | | | | |
| R945126 | 9999 | 9999 | | | | | | | | | | | | | |
| R945127 | 0.704 | 8.955 | | | | | | | | | | | | | |
| R945128 | 0.685 | 8.8 | | | | | | | | | | | | | |
| R945129 | 1.003 | >10 | | | | | | | | | | | | | |
| R945130 | 1.874 | 9999 | | | | | | | | | | | | | |
| R945131 | 0.77 | 9999 | | | | | | | | | | | | | |
| R945132 | 0.571 | 8.77 | | | | | | | | | | | | | |
| R945133 | 1.064 | >10 | | | | | | | | | | | | | |
| R945134 | 9999 | 9999 | | | | | | | | | | | | | |
| R945135 | 0.986 | 8.245 | | | | | | | | | | | | | |

TABLE 1

| Test Compound | Low Density | | | CHMC anti-IgE Hexos. | CHMC Ionomycin Hexos. | Basophils anti-IgE Histamine | Basophils Ionomycin Histamine | Basophils Dust mite Histamine | High Density | | | | | |
|---------------|------------------------|-------------------------|--------------------|----------------------|-----------------------|------------------------------|-------------------------------|-------------------------------|---------------------|-----------------------|-------------------------|--------------------|-------------------------|--------------------|
| | CHMC anti-IgE Tryptase | CHMC Ionomycin Tryptase | CHMC anti-IgE LTC4 | | | | | | BMMC anti-IgE hexos | BMMC Ionomycin Hexos. | BMMC anti-IgE histamine | BMMC anti-IgE LTC4 | BMMC anti-IgE TNF-alpha | BMMC anti-IgE IL-6 |
| R945137 | 1.649 | >10 | | | | | | | | | | | | |
| R945138 | 1.058 | 6.733 | | | | | | | | | | | | |
| R945139 | 1.016 | >10 | | | | | | | | | | | | |
| R945140 | 0.573 | >10 | | | | | | | | | | | | |
| R945142 | 1.049 | >10 | | | | | | | | | | | | |
| R945144 | 0.244 | 9999 | | | | | | | | | | | | |
| R945145 | 9999 | >10 | | | | | | | | | | | | |
| R945146 | 3.756 | 9999 | | | | | | | | | | | | |
| R945147 | 3.546 | 9999 | | | | | | | | | | | | |
| R945148 | 0.307 | 9999 | | | | | | | | | | | | |
| R945149 | 0.391 | >10 | | | | | | | | | | | | |
| R945150 | 0.467 | >10 | | | | | | | >2 | | >2 | 9999 | 0.709 | 0.634 |
| R945151 | 4.07 | 9999 | | | | | | | | | | | | |
| R945152 | 6.94 | 9999 | | | | | | | | | | | | |
| R945153 | 0.688 | 6.561 | | | | | | | | | | | | |
| R945155 | 1.878 | >10 | | | | | | | | | | | | |
| R945156 | 0.787 | 9999 | | | | | | | | | | | | |
| R945157 | 1.477 | 9999 | | | | | | | | | | | | |
| R945162 | 9999 | 9999 | | | | | | | | | | | | |
| R945163 | 0.922 | 4.251 | | | | | | | | | | | | |
| R945164 | 10 | 9999 | | | | | | | | | | | | |
| R945165 | 9999 | 9999 | | | | | | | | | | | | |
| R945166 | 9999 | 9999 | | | | | | | | | | | | |

TABLE 1

| Test Compound | Low Density | | | CHMC anti-IgE Hexos. | CHMC Ionomycin Hexos. | Basophils anti-IgE Histamine | Basophils Ionomycin Histamine | Basophils Dust mite Histamine | High Density | | | | | |
|---------------|------------------------|-------------------------|--------------------|----------------------|-----------------------|------------------------------|-------------------------------|-------------------------------|---------------------|-----------------------|-------------------------|--------------------|-------------------------|--------------------|
| | CHMC anti-IgE Tryptase | CHMC Ionomycin Tryptase | CHMC anti-IgE LTC4 | | | | | | BMMC anti-IgE hexos | BMMC Ionomycin Hexos. | BMMC anti-IgE histamine | BMMC anti-IgE LTC4 | BMMC anti-IgE TNF-alpha | BMMC anti-IgE IL-6 |
| R945167 | 0.761 | 9999 | | | | | | | | | | | | |
| R945168 | 10 | 9999 | | | | | | | | | | | | |
| R945169 | 10 | 9999 | | | | | | | | | | | | |
| R945170 | 0.661 | >10 | | | | | | | | | | | | |
| R945171 | 1.327 | 9999 | | | | | | | | | | | | |
| R945172 | 1.179 | 9999 | | | | | | | | | | | | |
| R945173 | 1.419 | 9999 | | | | | | | | | | | | |
| R945175 | 1.648 | 9999 | | | | | | | | | | | | |
| R950082 | 9999 | 9999 | | | | | | | | | | | | |
| R950083 | 9999 | 9999 | | | | | | | | | | | | |
| R950090 | 9999 | 9999 | | | | | | | | | | | | |
| R921302 | 0.37 | 9999 | | | | 0.19 | 9999 | 0.282 | | | | | | |
| R950092 | 9999 | 9999 | | | | | | | | | | | | |
| R950093 | 0.64 | 5.55 | | | | | | | | | | | | |
| R950100 | 0.71 | >10 | | | | | | | | | | | | |
| R950107 | 0.46 | >10 | | | | | | | | | | | | |
| R950108 | 2.075 | >10 | | | | | | | | | | | | |
| R950109 | 7.95 | | | | | | | | | | | | | |
| R950120 | 3 | 9999 | | | | | | | | | | | | |
| R950121 | 4.25 | >10 | | | | | | | | | | | | |
| R950122 | 3.025 | 9999 | | | | | | | | | | | | |
| R950123 | 3.25 | 8.45 | | | | | | | | | | | | |
| R950125 | 1.375 | 6.3 | | | | | | | | | | | | |

TABLE 1

| Test Compound | Low Density | | | | CHMC anti-IgE Hexos. | CHMC ionomycin Hexos. | Basophils anti-IgE Histamine | Basophils ionomycin Histamine | Basophils Dust mite Histamine | High Density | | | | | |
|------------------|------------------------------|-------------------------------|--------------------------|---------------------------|----------------------------|-----------------------------|------------------------------------|-------------------------------------|-------------------------------------|-----------------------------|-------------------------------|--------------------------|-------------------------------|--------------------------|--|
| | CHMC anti-IgE Tryptase | CHMC ionomycin Tryptase | CHMC anti-IgE LTC4 | BMMC anti-IgE hexos | | | | | | BMMC ionomycin Hexos. | BMMC anti-IgE histamine | BMMC anti-IgE LTC4 | BMMC anti-IgE TNF-alpha | BMMC anti-IgE IL-6 | |
| | | | | | | | | | | | | | | | |
| R950129 | 0.665 | >10 | | | | | | | | | | | | | |
| R950130 | 4.9 | | | | | | | | | | | | | | |
| R950131 | 9999 | | | | | | | | | | | | | | |
| R950132 | 9 | | | | | | | | | | | | | | |
| R950133 | 2.2 | >10 | | | | | | | | | | | | | |
| R950134 | 1.875 | 9999 | | | | | | | | | | | | | |
| R950135 | 0.85 | >10 | | | | | | | | | | | | | |
| R950137 | 2.23 | 9999 | | | | | | | | | | | | | |
| R950138 | 9.5 | | | | | | | | | | | | | | |
| R950139 | 1.375 | 9999 | | | | | | | | | | | | | |
| R950140 | 2.825 | 9999 | | | | | | | | | | | | | |
| R950141 | 0.31 | >10 | | | | | | | | | | | | | |
| R950142 | 10 | | | | | | | | | | | | | | |
| R950143 | 8.23 | | | | | | | | | | | | | | |
| R950144 | 10 | | | | | | | | | | | | | | |
| R950145 | 9999 | | | | | | | | | | | | | | |
| R950146 | 9999 | | | | | | | | | | | | | | |
| R950147 | 9999 | | | | | | | | | | | | | | |
| R950148 | 2.275 | 9999 | | | | | | | | | | | | | |
| R950149 | 10 | 9999 | | | | | | | | | | | | | |
| R950150 | 9999 | 9999 | | | | | | | | | | | | | |
| R950151 | 9999 | | | | | | | | | | | | | | |
| R950152 | 10 | | | | | | | | | | | | | | |

TABLE 1

| TABLE 1 | | | | | | | | | | | | | | | | |
|------------------|------------------------------|-------------------------------|--------------------------|---------------------------|----------------------------|-----------------------------|------------------------------------|-------------------------------------|-------------------------------------|-----------------------------|-------------------------------|--------------------------|-------------------------------|--------------------------|--|--|
| Test Compound | Low Density | | | | CHMC anti-IgE Hexos. | CHMC Ionomycin Hexos. | Basophils anti-IgE Histamine | Basophils Ionomycin Histamine | Basophils Dust mite Histamine | High Density | | | | | | |
| | CHMC anti-IgE Tryptase | CHMC Ionomycin Tryptase | CHMC anti-IgE LTC4 | BMMC anti-IgE hexos | | | | | | BMMC Ionomycin Hexos. | BMMC anti-IgE histamine | BMMC anti-IgE LTC4 | BMMC anti-IgE TNF-alpha | BMMC anti-IgE IL-6 | | |
| | | | | | | | | | | | | | | | | |
| R950153 | 9999 | | | | | | | | | | | | | | | |
| R950154 | 2.075 | 9999 | | | | | | | | | | | | | | |
| R950155 | 9999 | | | | | | | | | | | | | | | |
| R950156 | 9999 | | | | | | | | | | | | | | | |
| R950157 | 9999 | | | | | | | | | | | | | | | |
| R950158 | 9.98 | | | | | | | | | | | | | | | |
| R950159 | 0.61 | 9999 | | | | | | | | | | | | | | |
| R950160 | 1 | 9999 | | | | | | | | | | | | | | |
| R950162 | 0.434 | >10 | | | | | | | | | | | | | | |
| R950163 | 0.874 | 9999 | | | | | | | | | | | | | | |
| R950164 | 1.893 | 9999 | | | | | | | | | | | | | | |
| R950165 | 1.288 | 9999 | | | | | | | | | | | | | | |
| R950166 | 1.889 | 9999 | | | | | | | | | | | | | | |
| R950167 | 9999 | 9999 | | | | | | | | | | | | | | |
| R950168 | 6.496 | 8.653 | | | | | | | | | | | | | | |
| R950169 | 1.273 | 9.518 | | | | | | | | | | | | | | |
| R950170 | 9999 | 9999 | | | | | | | | | | | | | | |
| R950171 | 0.585 | >10 | | | | | | | | | | | | | | |
| R950172 | 0.983 | 9999 | | | | | | | | | | | | | | |
| R950173 | 2.368 | >10 | | | | | | | | | | | | | | |
| R950174 | 4.618 | 9999 | | | | | | | | | | | | | | |
| R950175 | 1.688 | 9999 | | | | | | | | | | | | | | |
| R950176 | 1.342 | 9999 | | | | | | | | | | | | | | |

TABLE 1

| TABLE 1 | | | | | | | | | | | | | | | | |
|------------------|------------------------------|-------------------------------|--------------------------|---------------------------|----------------------------|-----------------------------|------------------------------------|-------------------------------------|-------------------------------------|-----------------------------|-------------------------------|--------------------------|-------------------------------|--------------------------|-------|--|
| Test Compound | Low Density | | | | CHMC anti-IgE Hexos. | CHMC ionomycin Hexos. | Basophils anti-IgE Histamine | Basophils ionomycin Histamine | Basophils Dust mite Histamine | High Density | | | | | | |
| | CHMC anti-IgE Tryptase | CHMC ionomycin Tryptase | CHMC anti-IgE LTC4 | BMMC anti-IgE hexos | | | | | | BMMC ionomycin Hexos. | BMMC anti-IgE histamine | BMMC anti-IgE LTC4 | BMMC anti-IgE TNF-alpha | BMMC anti-IgE IL-6 | | |
| | | | | | | | | | | | | | | | | |
| R950177 | 2.361 | 8.434 | | | | | | | | | | | | | | |
| R950178 | 0.688 | >10 | | | | | | | | | | | | | | |
| R950179 | 0.955 | >10 | | | | | | | | | | | | | | |
| R950180 | 0.278 | 9999 | | | | | | | | | | | | | | |
| R950181 | 0.254 | 9999 | | | | | | | | | | | | | | |
| R950182 | 0.627 | 9999 | | | | | | | | | | | | | | |
| R950183 | 4.797 | 9999 | | | | | | | | | | | | | | |
| R950184 | 2.222 | 9999 | | | | | | | | | | | | | | |
| R950185 | 1.03 | 8.81 | | | | | | | | | | | | | | |
| R950186 | 0.558 | >10 | | | | | | | | | | | | | | |
| R950187 | 0.724 | >10 | | | | | | | | | | | | | | |
| R950188 | 2.327 | 9999 | | | | | | | | | | | | | | |
| R950189 | 10 | 9999 | | | | | | | | | | | | | | |
| R950190 | 1.573 | 9999 | | | | | | | | | | | | | | |
| R950191 | 0.178 | 9999 | | | | | | | | | <0.22 | >2 | 0.401 | <0.22 | <0.22 | |
| R950192 | 0.244 | 9999 | | | | | | | | | | | | | | |
| R950193 | 0.61 | 9999 | | | | | | | | | | | | | | |
| R950194 | 2.04 | 9999 | | | | | | | | | | | | | | |
| R950195 | 0.473 | 9999 | | | | | | | | | | | | | | |
| R950196 | 2.2 | 9999 | | | | | | | | | | | | | | |
| R950197 | 0.531 | 9999 | | | | | | | | | | | | | | |
| R950198 | 0.406 | >10 | | | | | | | | | | | | | | |
| R950199 | 0.408 | 9999 | | | | | | | | | | | | | | |

TABLE 1

| TABLE 1 | | | | | | | | | | | | | | | | |
|------------------|------------------------------|-------------------------------|--------------------------|---------------------------|----------------------------|-----------------------------|------------------------------------|-------------------------------------|-------------------------------------|-----------------------------|-------------------------------|--------------------------|-------------------------------|--------------------------|-------|-------|
| Test Compound | Low Density | | | | CHMC anti-IgE Hexos. | CHMC ionomycin Hexos. | Basophils anti-IgE Histamine | Basophils ionomycin Histamine | Basophils Dust mite Histamine | High Density | | | | | | |
| | CHMC anti-IgE Tryptase | CHMC ionomycin Tryptase | CHMC anti-IgE LTC4 | BMMC anti-IgE hexos | | | | | | BMMC ionomycin Hexos. | BMMC anti-IgE histamine | BMMC anti-IgE LTC4 | BMMC anti-IgE TNF-alpha | BMMC anti-IgE IL-6 | | |
| | | | | | | | | | | | | | | | | |
| R950200 | 0.245 | 9999 | | | | | | | | | | | | | | |
| R950201 | 0.261 | 9999 | | | | | | | | | | | | | | |
| R950202 | 3.218 | 9999 | | | | | | | | | | | | | | |
| R950203 | 9.035 | 9999 | | | | | | | | | | | | | | |
| R950204 | 6.285 | 9999 | | | | | | | | | | | | | | |
| R950205 | 8.997 | 9999 | | | | | | | | | | | | | | |
| R950206 | 3.66 | >10 | | | | | | | | | | | | | | |
| R950207 | 0.164 | 9999 | | | | | | | | | <0.22 | <0.22 | 0.288 | <0.22 | <0.22 | <0.22 |
| R950208 | 0.267 | 9999 | | | | | | | | | | | | | | |
| R950209 | 0.748 | 9999 | | | | | | | | | | | | | | |
| R950210 | 10 | 9999 | | | | | | | | | | | | | | |
| R950211 | 10 | 9999 | | | | | | | | | | | | | | |
| R950212 | 0.253 | 9999 | | | | | | | | | | | | | | |
| R950213 | 9999 | 9999 | | | | | | | | | | | | | | |
| R950214 | 10 | 9999 | | | | | | | | | | | | | | |
| R950215 | 0.409 | 9999 | | | | | | | | | | | | | | |
| R950216 | 0.327 | 9999 | | | | | | | | | | | | | | |
| R950217 | 0.34 | 9999 | | | | | | | | | | | | | | |
| R950218 | 0.292 | 9999 | | | | | | | | | | | | | | |
| R950219 | 0.439 | 9999 | | | | | | | | | | | | | | |
| R950220 | 0.489 | 9999 | | | | | | | | | | | | | | |
| R950221 | 0.636 | 9999 | | | | | | | | | | | | | | |
| R950222 | 0.865 | 9999 | | | | | | | | | | | | | | |

TABLE 1

| TABLE 1 | | | | | | | | | | | | | | | | |
|------------------|------------------------------|-------------------------------|--------------------------|---------------------------|----------------------------|-----------------------------|------------------------------------|-------------------------------------|-------------------------------------|-----------------------------|-------------------------------|--------------------------|-------------------------------|--------------------------|--|--|
| Test Compound | Low Density | | | | CHMC anti-IgE Hexos. | CHMC ionomycin Hexos. | Basophils anti-IgE Histamine | Basophils ionomycin Histamine | Basophils Dust mite Histamine | High Density | | | | | | |
| | CHMC anti-IgE Tryptase | CHMC ionomycin Tryptase | CHMC anti-IgE LTC4 | BMMC anti-IgE hexos | | | | | | BMMC ionomycin Hexos. | BMMC anti-IgE histamine | BMMC anti-IgE LTC4 | BMMC anti-IgE TNF-alpha | BMMC anti-IgE IL-6 | | |
| | | | | | | | | | | | | | | | | |
| R950223 | 0.763 | 9999 | | | | | | | | | | | | | | |
| R950224 | 0.687 | 9999 | | | | | | | | | | | | | | |
| R950225 | 5.283 | 9999 | | | | | | | | | | | | | | |
| R950226 | 1.374 | 9999 | | | | | | | | | | | | | | |
| R950227 | 1.029 | 9999 | | | | | | | | | | | | | | |
| R950229 | 0.98 | 9999 | | | | | | | | | | | | | | |
| R950230 | 7.91 | 9999 | | | | | | | | | | | | | | |
| R950231 | 1.968 | 9999 | | | | | | | | | | | | | | |
| R950232 | 10 | 9999 | | | | | | | | | | | | | | |
| R950233 | 0.98 | 9999 | | | | | | | | | | | | | | |
| R950234 | 10 | 9999 | | | | | | | | | | | | | | |
| R950235 | 4.095 | 9999 | | | | | | | | | | | | | | |
| R950236 | 0.955 | 9999 | | | | | | | | | | | | | | |
| R950237 | 9999 | 9999 | | | | | | | | | | | | | | |
| R950238 | 10 | 9999 | | | | | | | | | | | | | | |
| R950239 | 2.063 | 9999 | | | | | | | | | | | | | | |
| R950240 | 1.766 | 9999 | | | | | | | | | | | | | | |
| R950241 | 3.275 | 9999 | | | | | | | | | | | | | | |
| R950251 | 9999 | 9999 | | | | | | | | | | | | | | |
| R950253 | 0.697 | 9999 | | | | | | | | | | | | | | |
| R950254 | 0.496 | 9999 | | | | | | | | | | | | | | |
| R950255 | 10 | 9999 | | | | | | | | | | | | | | |
| R908698 | 1.67 | 9999 | | | | | | | | | | | | | | |

TABLE 1

| TABLE 1 | | | | | | | | | | | | | | | | |
|------------------|------------------------------|-------------------------------|--------------------------|---------------------------|----------------------------|-----------------------------|------------------------------------|-------------------------------------|-------------------------------------|-----------------------------|-------------------------------|--------------------------|-------------------------------|--------------------------|--|--|
| Test Compound | Low Density | | | | CHMC anti-IgE Hexos. | CHMC Ionomycin Hexos. | Basophils anti-IgE Histamine | Basophils Ionomycin Histamine | Basophils Dust mite Histamine | High Density | | | | | | |
| | CHMC anti-IgE Tryptase | CHMC Ionomycin Tryptase | CHMC anti-IgE LTC4 | BMMC anti-IgE hexos | | | | | | BMMC Ionomycin Hexos. | BMMC anti-IgE histamine | BMMC anti-IgE LTC4 | BMMC anti-IgE TNF-alpha | BMMC anti-IgE IL-6 | | |
| | | | | | | | | | | | | | | | | |
| R908699 | 0.217 | 9999 | | | | | | | | | | | | | | |
| R908700 | 1.273 | 9999 | | | | | | | | | | | | | | |
| R908701 | 0.099 | 7.643 | | | | | | | | | | | | | | |
| R908702 | 0.104 | 7.395 | | | | | | | | | | | | | | |
| R908703 | 0.63 | 9999 | | | | | | | | | | | | | | |
| R908704 | 0.511 | 9999 | | | | | | | | | | | | | | |
| R908705 | 0.801 | 9999 | | | | | | | | | | | | | | |
| R908706 | 0.445 | 9999 | | | | | | | | | | | | | | |
| R908707 | 1.834 | 9999 | | | | | | | | | | | | | | |
| R908709 | 2.414 | | | | | | | | | | | | | | | |
| R908710 | 1.838 | 99 | | | | | | | | | | | | | | |
| R908711 | 1.761 | | | | | | | | | | | | | | | |
| R908712 | 0.075 | 99 | | | | | | | | | | | | | | |
| R908734 | 1.379 | | | | | | | | | | | | | | | |
| R909255 | 0.244 | 9999 | | | | | | | | | | | | | | |
| R909259 | 0.43 | 9999 | | | | | | | | | | | | | | |
| R909260 | 1.041 | 9999 | | | | | | | | | | | | | | |
| R909261 | 0.93 | 9999 | | | | | | | | | | | | | | |
| R909263 | 0.289 | 9999 | | | | | | | | | | | | | | |
| R909264 | | | | | | | | | | | | | | | | |
| R909265 | 99 | | | | | | | | | | | | | | | |
| R909266 | 99 | | | | | | | | | | | | | | | |
| R909267 | 0.589 | 9999 | | | | | | | | | | | | | | |

TABLE 1

| Test Compound | Low Density | | | | CHMC anti-IgE Hexos. | CHMC ionomycin Hexos. | Basophils anti-IgE Histamine | Basophils ionomycin Histamine | Basophils Dust mite Histamine | High Density | | | | | |
|------------------|------------------------------|-------------------------------|--------------------------|---------------------------|----------------------------|-----------------------------|------------------------------------|-------------------------------------|-------------------------------------|-----------------------------|-------------------------------|--------------------------|-------------------------------|--------------------------|--|
| | CHMC anti-IgE Tryptase | CHMC ionomycin Tryptase | CHMC anti-IgE LTC4 | BMMC anti-IgE hexos | | | | | | BMMC ionomycin Hexos. | BMMC anti-IgE histamine | BMMC anti-IgE LTC4 | BMMC anti-IgE TNF-alpha | BMMC anti-IgE IL-6 | |
| | | | | | | | | | | | | | | | |
| R909268 | 0.071 | 9999 | | | | | | | | | | | | | |
| R909290 | 0.226 | | | | | | | | | | | | | | |
| R909292 | 1.172 | | | | | | | | | | | | | | |
| R909308 | 0.671 | 9999 | | | | | | | | | | | | | |
| R909309 | 0.083 | 9999 | | | | | | | | | | | | | |
| R920394 | | | | | | | | | | | | | | | |
| R920395 | 0.092 | 9999 | | | | | | | | | | | | | |
| R920396 | | | | | | | | | | | | | | | |
| R920397 | | | | | | | | | | | | | | | |
| R920398 | | | | | | | | | | | | | | | |
| R920399 | | | | | | | | | | | | | | | |
| R920404 | | | | | | | | | | | | | | | |
| R920405 | | | | | | | | | | | | | | | |
| R920406 | | | | | | | | | | | | | | | |
| R920407 | | | | | | | | | | | | | | | |
| R920408 | | | | | | | | | | | | | | | |
| R920410 | 0.125 | 9999 | | | | | | | | | | | | | |
| R920411 | 0.564 | 9999 | | | | | | | | | | | | | |
| R925745 | 1.766 | 9999 | | | | | | | | | | | | | |
| R926238 | 9999 | | | | | | | | | | | | | | |
| R926752 | 0.338 | 9999 | | | | | | | | | | | | | |
| R926753 | 0.108 | 9999 | | | | | | | | | | | | | |
| R926754 | 0.388 | 9999 | | | | | | | | | | | | | |

TABLE 1

| TABLE 1 | | | | | | | | | | | | | | | | | |
|---------------|------------------------|-------------------------|--------------------|----------------------|-----------------------|------------------------------|-------------------------------|-------------------------------|---------------------|-----------------------|-------------------------|--------------------|-------------------------|--------------------|--|--|--|
| Test Compound | Low Density | | | CHMC anti-IgE Hexos. | CHMC Ionomycin Hexos. | Basophils anti-IgE Histamine | Basophils Ionomycin Histamine | Basophils Dust mite Histamine | High Density | | | | | | | | |
| | CHMC anti-IgE Tryptase | CHMC Ionomycin Tryptase | CHMC anti-IgE LTC4 | | | | | | BMMC anti-IgE hexos | BMMC Ionomycin Hexos. | BMMC anti-IgE histamine | BMMC anti-IgE LTC4 | BMMC anti-IgE TNF-alpha | BMMC anti-IgE IL-6 | | | |
| R926755 | 1.693 | 9999 | | | | | | | | | | | | | | | |
| R926756 | 1.365 | 9999 | | | | | | | | | | | | | | | |
| R926757 | 0.158 | 9999 | | | | | | | | | | | | | | | |
| R926759 | 0.688 | 9999 | | | | | | | | | | | | | | | |
| R926760 | 2.893 | 9999 | | | | | | | | | | | | | | | |
| R926761 | 0.245 | 9999 | | | | | | | | | | | | | | | |
| R926762 | 0.386 | 9999 | | | | | | | | | | | | | | | |
| R926763 | 0.195 | 9999 | | | | | | | | | | | | | | | |
| R926794 | 1.382 | 9999 | | | | | | | | | | | | | | | |
| R926826 | 0.613 | 9999 | | | | | | | | | | | | | | | |
| R926827 | 1.098 | 9999 | | | | | | | | | | | | | | | |
| R926828 | 0.306 | 9999 | | | | | | | | | | | | | | | |
| R926829 | 0.688 | 9999 | | | | | | | | | | | | | | | |
| R926830 | 0.569 | 10 | | | | | | | | | | | | | | | |
| R926831 | 0.133 | 10 | | | | | | | | | | | | | | | |
| R926832 | 0.365 | 9999 | | | | | | | | | | | | | | | |
| R926833 | 1.129 | 9999 | | | | | | | | | | | | | | | |
| R926834 | 0.145 | 9999 | | | | | | | | | | | | | | | |
| R926835 | 0.296 | 9999 | | | | | | | | | | | | | | | |
| R926836 | 10 | 9999 | | | | | | | | | | | | | | | |
| R926837 | 2.994 | 9999 | | | | | | | | | | | | | | | |
| R926838 | 0.583 | 9999 | | | | | | | | | | | | | | | |
| R926839 | 0.161 | 9999 | | | | | | | | | | | | | | | |

TABLE 1

| Test Compound | Low Density | | | CHMC anti-IgE Hexos. | CHMC anti-IgE Hexos. | CHMC Ionomycin Hexos. | Basophils anti-IgE Histamine | Basophils Ionomycin Histamine | Basophils Dust mite Histamine | High Density | | | | | |
|------------------|------------------------------|-------------------------------|--------------------------|----------------------------|----------------------------|-----------------------------|------------------------------------|-------------------------------------|-------------------------------------|---------------------------|-----------------------------|-------------------------------|--------------------------|-------------------------------|--------------------------|
| | CHMC anti-IgE Tryptase | CHMC Ionomycin Tryptase | CHMC anti-IgE LTC4 | | | | | | | BMMC anti-IgE hexos | BMMC Ionomycin Hexos. | BMMC anti-IgE histamine | BMMC anti-IgE LTC4 | BMMC anti-IgE TNF-alpha | BMMC anti-IgE IL-6 |
| R926840 | 1.1 | 9999 | | | | | | | | | | | | | |
| R926841 | 0.551 | 9999 | | | | | | | | | | | | | |
| R926842 | 7.733 | 9999 | | | | | | | | | | | | | |
| R926843 | 7.371 | 9999 | | | | | | | | | | | | | |
| R926844 | 1.1 | 9999 | | | | | | | | | | | | | |
| R926845 | 2.558 | 7.812 | | | | | | | | | | | | | |
| R926846 | 0.86 | 6.264 | | | | | | | | | | | | | |
| R926847 | 1.479 | 6.264 | | | | | | | | | | | | | |
| R926848 | 0.254 | 10 | | | | | | | | | | | | | |
| R926851 | 0.446 | | | | | | | | | | | | | | |
| R926855 | 9999 | 9999 | | | | | | | | | | | | | |
| R926856 | 0.734 | 9999 | | | | | | | | | | | | | |
| R926857 | 1.209 | 9999 | | | | | | | | | | | | | |
| R926859 | | | | | | | | | | | | | | | |
| R926860 | 1.949 | 99 | | | | | | | | | | | | | |
| R926862 | 0.774 | 9999 | | | | | | | | | | | | | |
| R926863 | | | | | | | | | | | | | | | |
| R926866 | | | | | | | | | | | | | | | |
| R926870 | 3.294 | | | | | | | | | | | | | | |
| R926871 | 2.146 | | | | | | | | | | | | | | |
| R926874 | 0.638 | 9999 | | | | | | | | | | | | | |
| R926879 | 0.397 | 9999 | | | | | | | | | | | | | |
| R926880 | | | | | | | | | | | | | | | |

TABLE 1

| Test Compound | Low Density | | | CHMC anti-IgE Hexos. | CHMC ionomycin Hexos. | Basophils anti-IgE Histamine | Basophils ionomycin Histamine | Basophils Dust mite Histamine | High Density | | | | | |
|------------------|------------------------------|-------------------------------|--------------------------|----------------------------|-----------------------------|------------------------------------|-------------------------------------|-------------------------------------|---------------------------|-----------------------------|-------------------------------|--------------------------|-------------------------------|--------------------------|
| | CHMC anti-IgE Tryptase | CHMC ionomycin Tryptase | CHMC anti-IgE LTC4 | | | | | | BMMC anti-IgE hexos | BMMC ionomycin Hexos. | BMMC anti-IgE histamine | BMMC anti-IgE LTC4 | BMMC anti-IgE TNF-alpha | BMMC anti-IgE IL-6 |
| R926881 | | | | | | | | | | | | | | |
| R926883 | | | | | | | | | | | | | | |
| R926885 | | | | | | | | | | | | | | |
| R926886 | | | | | | | | | | | | | | |
| R926887 | 1.747 | | | | | | | | | | | | | |
| R926890 | 0.361 | 9999 | | | | | | | | | | | | |
| R926891 | 0.152 | 9999 | | | | | | | | | | | | |
| R926892 | 0.685 | 9999 | | | | | | | | | | | | |
| R926893 | 10 | 9999 | | | | | | | | | | | | |
| R926894 | 9999 | 9999 | | | | | | | | | | | | |
| R926895 | 0.339 | 9999 | | | | | | | | | | | | |
| R926896 | 1.622 | 9999 | | | | | | | | | | | | |
| R926897 | 1.727 | 9999 | | | | | | | | | | | | |
| R926898 | 1.1 | 9999 | | | | | | | | | | | | |
| R926899 | 1.1 | 9999 | | | | | | | | | | | | |
| R926900 | 9999 | 9999 | | | | | | | | | | | | |
| R926902 | 1.37 | 4.586 | | | | | | | | | | | | |
| R926903 | 0.243 | 9999 | | | | | | | | | | | | |
| R926904 | 0.538 | | | | | | | | | | | | | |
| R926905 | 99 | | | | | | | | | | | | | |
| R926906 | 0.794 | | | | | | | | | | | | | |
| R926907 | 0.764 | | | | | | | | | | | | | |
| R926908 | 0.585 | | | | | | | | | | | | | |

TABLE 1

| TABLE 1 | | | | | | | | | | | | | | | |
|---------------|------------------------|-------------------------|--------------------|---------------------|----------------------|-----------------------|------------------------------|-------------------------------|-------------------------------|-----------------------|-------------------------|--------------------|-------------------------|--------------------|--|
| Test Compound | Low Density | | | | CHMC anti-IgE Hexos. | CHMC Ionomycin Hexos. | Basophils anti-IgE Histamine | Basophils Ionomycin Histamine | Basophils Dust mite Histamine | High Density | | | | | |
| | CHMC anti-IgE Tryptase | CHMC Ionomycin Tryptase | CHMC anti-IgE LTC4 | BMMC anti-IgE hexos | | | | | | BMMC Ionomycin Hexos. | BMMC anti-IgE histamine | BMMC anti-IgE LTC4 | BMMC anti-IgE TNF-alpha | BMMC anti-IgE IL-6 | |
| | | | | | | | | | | | | | | | |
| R926909 | 0.379 | | | | | | | | | | | | | | |
| R926913 | 0.548 | 9999 | | | | | | | | | | | | | |
| R926914 | 1.86 | 9999 | | | | | | | | | | | | | |
| R926915 | 1.713 | 9999 | | | | | | | | | | | | | |
| R926916 | 1.958 | 9999 | | | | | | | | | | | | | |
| R926917 | 1.169 | 9999 | | | | | | | | | | | | | |
| R926918 | 2.521 | 9999 | | | | | | | | | | | | | |
| R926919 | 1.413 | 9999 | | | | | | | | | | | | | |
| R926922 | 0.305 | 9999 | | | | | | | | | | | | | |
| R926923 | 0.346 | 9999 | | | | | | | | | | | | | |
| R926925 | 0.307 | 99 | | | | | | | | | | | | | |
| R926926 | 0.401 | 9999 | | | | | | | | | | | | | |
| R926927 | 0.348 | 9999 | | | | | | | | | | | | | |
| R926928 | 0.575 | 9999 | | | | | | | | | | | | | |
| R926929 | 1.916 | 9999 | | | | | | | | | | | | | |
| R926930 | 99 | 9999 | | | | | | | | | | | | | |
| R926931 | | | | | | | | | | | | | | | |
| R926932 | 0.31 | 9999 | | | | | | | | | | | | | |
| R926933 | | | | | | | | | | | | | | | |
| R926934 | | | | | | | | | | | | | | | |
| R926935 | 4.44 | | | | | | | | | | | | | | |
| R926936 | | | | | | | | | | | | | | | |
| R926937 | | | | | | | | | | | | | | | |

TABLE 1

| TABLE 1 | | | | | | | | | | | | | | | | | |
|------------------|------------------------------|-------------------------------|--------------------------|---------------------------|----------------------------|-----------------------------|------------------------------------|-------------------------------------|-------------------------------------|-----------------------------|-------------------------------|--------------------------|-------------------------------|--------------------------|--|--|--|
| Test Compound | Low Density | | | | CHMC anti-IgE Hexos. | CHMC ionomycin Hexos. | Basophils anti-IgE Histamine | Basophils ionomycin Histamine | Basophils Dust mite Histamine | High Density | | | | | | | |
| | CHMC anti-IgE Tryptase | CHMC ionomycin Tryptase | CHMC anti-IgE LTC4 | BMMC anti-IgE hexos | | | | | | BMMC ionomycin Hexos. | BMMC anti-IgE histamine | BMMC anti-IgE LTC4 | BMMC anti-IgE TNF-alpha | BMMC anti-IgE IL-6 | | | |
| | | | | | | | | | | | | | | | | | |
| R926938 | | | | | | | | | | | | | | | | | |
| R926939 | 3.615 | | | | | | | | | | | | | | | | |
| R926940 | 7.754 | | | | | | | | | | | | | | | | |
| R926941 | 4.195 | | | | | | | | | | | | | | | | |
| R926942 | 4.81 | | | | | | | | | | | | | | | | |
| R926943 | | | | | | | | | | | | | | | | | |
| R926944 | 0.225 | 99 | | | | | | | | | | | | | | | |
| R926945 | 0.457 | 9999 | | | | | | | | | | | | | | | |
| R926946 | | | | | | | | | | | | | | | | | |
| R926947 | 0.354 | 9999 | | | | | | | | | | | | | | | |
| R926948 | 0.246 | 9999 | | | | | | | | | | | | | | | |
| R926949 | 0.089 | 9999 | | | | | | | | | | | | | | | |
| R926950 | 99 | 9999 | | | | | | | | | | | | | | | |
| R926951 | 0.183 | 9999 | | | | | | | | | | | | | | | |
| R926953 | 0.049 | 9999 | | | | | | | | | | | | | | | |
| R926954 | 0.284 | 9999 | | | | | | | | | | | | | | | |
| R926955 | 0.36 | 9999 | | | | | | | | | | | | | | | |
| R926956 | 0.211 | 9999 | | | | | | | | | | | | | | | |
| R927016 | 1.408 | | | | | | | | | | | | | | | | |
| R927017 | 2.449 | | | | | | | | | | | | | | | | |
| R927018 | 1.446 | | | | | | | | | | | | | | | | |
| R927019 | 1.179 | | | | | | | | | | | | | | | | |
| R927020 | 1.316 | 9999 | | | | | | | | | | | | | | | |

TABLE 1

| TABLE 1 | | | | | | | | | | | | | | | | |
|------------------|------------------------------|-------------------------------|--------------------------|---------------------------|----------------------------|-----------------------------|------------------------------------|-------------------------------------|-------------------------------------|-----------------------------|-------------------------------|--------------------------|-------------------------------|--------------------------|--|--|
| Test Compound | Low Density | | | | CHMC anti-IgE Hexos. | CHMC Ionomycin Hexos. | Basophils anti-IgE Histamine | Basophils Ionomycin Histamine | Basophils Dust mite Histamine | High Density | | | | | | |
| | CHMC anti-IgE Tryptase | CHMC Ionomycin Tryptase | CHMC anti-IgE LTC4 | BMMC anti-IgE hexos | | | | | | BMMC Ionomycin Hexos. | BMMC anti-IgE histamine | BMMC anti-IgE LTC4 | BMMC anti-IgE TNF-alpha | BMMC anti-IgE IL-6 | | |
| | | | | | | | | | | | | | | | | |
| R927023 | 0.918 | 9999 | | | | | | | | | | | | | | |
| R935221 | 9999 | 9999 | | | | | | | | | | | | | | |
| R935222 | 0.52 | 9999 | | | | | | | | | | | | | | |
| R935223 | 0.469 | 9999 | | | | | | | | | | | | | | |
| R935224 | 4.578 | 9999 | | | | | | | | | | | | | | |
| R935225 | 6.495 | 9999 | | | | | | | | | | | | | | |
| R935237 | 0.24 | 9999 | | | | | | | | | | | | | | |
| R935238 | 1.854 | 9999 | | | | | | | | | | | | | | |
| R935239 | 0.609 | 9999 | | | | | | | | | | | | | | |
| R935240 | 0.606 | 9999 | | | | | | | | | | | | | | |
| R935242 | 2.855 | 9999 | | | | | | | | | | | | | | |
| R935248 | 1.1 | 9999 | | | | | | | | | | | | | | |
| R935249 | 1.1 | 9999 | | | | | | | | | | | | | | |
| R935250 | 1.1 | 9999 | | | | | | | | | | | | | | |
| R935251 | | | | | | | | | | | | | | | | |
| R935252 | | | | | | | | | | | | | | | | |
| R935253 | | | | | | | | | | | | | | | | |
| R935255 | 0.374 | 9999 | | | | | | | | | | | | | | |
| R935256 | 0.324 | 9999 | | | | | | | | | | | | | | |
| R935258 | 1.191 | 9999 | | | | | | | | | | | | | | |
| R935259 | 1.777 | 9999 | | | | | | | | | | | | | | |
| R935261 | 0.391 | 9999 | | | | | | | | | | | | | | |
| R935262 | 0.516 | 9999 | | | | | | | | | | | | | | |

TABLE 1

| TABLE 1 | | | | | | | | | | | | | | | | |
|---------------|------------------------|-------------------------|--------------------|---------------------|----------------------|-----------------------|------------------------------|-------------------------------|-------------------------------|-----------------------|-------------------------|--------------------|-------------------------|--------------------|--|--|
| Test Compound | Low Density | | | | CHMC anti-IgE Hexos. | CHMC Ionomycin Hexos. | Basophils anti-IgE Histamine | Basophils Ionomycin Histamine | Basophils Dust mite Histamine | High Density | | | | | | |
| | CHMC anti-IgE Tryptase | CHMC Ionomycin Tryptase | CHMC anti-IgE LTC4 | BMMC anti-IgE hexos | | | | | | BMMC Ionomycin Hexos. | BMMC anti-IgE histamine | BMMC anti-IgE LTC4 | BMMC anti-IgE TNF-alpha | BMMC anti-IgE IL-6 | | |
| | | | | | | | | | | | | | | | | |
| R935263 | 0.106 | 10 | | | | | | | | | | | | | | |
| R935264 | 0.135 | 9999 | | | | | | | | | | | | | | |
| R935266 | 2.97 | | | | | | | | | | | | | | | |
| R935267 | 2.463 | | | | | | | | | | | | | | | |
| R935268 | 1.059 | | | | | | | | | | | | | | | |
| R935269 | 1.715 | | | | | | | | | | | | | | | |
| R935271 | | | | | | | | | | | | | | | | |
| R935276 | 2.33 | | | | | | | | | | | | | | | |
| R935277 | 22.883 | 8.9 | | | | | | | | | | | | | | |
| R935278 | 4.753 | 9999 | | | | | | | | | | | | | | |
| R935279 | 0.889 | 9999 | | | | | | | | | | | | | | |
| R935280 | 99 | | | | | | | | | | | | | | | |
| R935281 | 1.399 | 9999 | | | | | | | | | | | | | | |
| R935286 | 1.158 | 9999 | | | | | | | | | | | | | | |
| R935287 | 0.403 | 9999 | | | | | | | | | | | | | | |
| R935288 | 1.58 | 9999 | | | | | | | | | | | | | | |
| R935289 | 1.688 | 9999 | | | | | | | | | | | | | | |
| R935290 | 0.34 | 9999 | | | | | | | | | | | | | | |
| R935291 | 1.364 | 9999 | | | | | | | | | | | | | | |
| R935292 | 0.483 | 9999 | | | | | | | | | | | | | | |
| R935293 | 0.141 | 9999 | | | | | | | | | | | | | | |
| R935294 | 0.388 | 9999 | | | | | | | | | | | | | | |
| R935295 | 1.943 | 9999 | | | | | | | | | | | | | | |

TABLE 1

| TABLE 1 | | | | | | | | | | | | | | | | |
|---------------|------------------------|-------------------------|--------------------|---------------------|----------------------|-----------------------|------------------------------|-------------------------------|-------------------------------|-----------------------|-------------------------|--------------------|-------------------------|--------------------|--|--|
| Test Compound | Low Density | | | | CHMC anti-IgE Hexos. | CHMC Ionomycin Hexos. | Basophils anti-IgE Histamine | Basophils Ionomycin Histamine | Basophils Dust mite Histamine | High Density | | | | | | |
| | CHMC anti-IgE Tryptase | CHMC Ionomycin Tryptase | CHMC anti-IgE LTC4 | BMMC anti-IgE hexos | | | | | | BMMC Ionomycin Hexos. | BMMC anti-IgE histamine | BMMC anti-IgE LTC4 | BMMC anti-IgE TNF-alpha | BMMC anti-IgE IL-6 | | |
| | | | | | | | | | | | | | | | | |
| R935296 | 99 | 9999 | | | | | | | | | | | | | | |
| R935297 | 7.328 | 9999 | | | | | | | | | | | | | | |
| R935298 | 0.252 | 99 | | | | | | | | | | | | | | |
| R935299 | 0.21 | 9999 | | | | | | | | | | | | | | |
| R935300 | 0.243 | 9999 | | | | | | | | | | | | | | |
| R935301 | 4.05 | 99 | | | | | | | | | | | | | | |
| R935302 | 0.189 | 9999 | | | | | | | | | | | | | | |
| R935303 | 0.244 | 99 | | | | | | | | | | | | | | |
| R935304 | 0.188 | 9999 | | | | | | | | | | | | | | |
| R935305 | 0.495 | 9999 | | | | | | | | | | | | | | |
| R935306 | 0.345 | 99 | | | | | | | | | | | | | | |
| R935307 | 0.139 | 99 | | | | | | | | | | | | | | |
| R935308 | 0.275 | 9999 | | | | | | | | | | | | | | |
| R935309 | | | | | | | | | | | | | | | | |
| R935310 | | | | | | | | | | | | | | | | |
| R935320 | 2.769 | | | | | | | | | | | | | | | |
| R935321 | 2.986 | | | | | | | | | | | | | | | |
| R935322 | 3.416 | | | | | | | | | | | | | | | |
| R935323 | 9999 | | | | | | | | | | | | | | | |
| R935324 | 9999 | | | | | | | | | | | | | | | |
| R935336 | 0.341 | 9999 | | | | | | | | | | | | | | |
| R935337 | 9999 | | | | | | | | | | | | | | | |
| R935338 | 0.411 | 9999 | | | | | | | | | | | | | | |

TABLE 1

| TABLE 1 | | | | | | | | | | | | | | | | |
|------------------|------------------------------|-------------------------------|--------------------------|---------------------------|----------------------------|-----------------------------|------------------------------------|-------------------------------------|-------------------------------------|-----------------------------|-------------------------------|--------------------------|-------------------------------|--------------------------|--|--|
| Test Compound | Low Density | | | | CHMC anti-IgE Hexos. | CHMC Ionomycin Hexos. | Basophils anti-IgE Histamine | Basophils Ionomycin Histamine | Basophils Dust mite Histamine | High Density | | | | | | |
| | CHMC anti-IgE Tryptase | CHMC Ionomycin Tryptase | CHMC anti-IgE LTC4 | BMMC anti-IgE hexos | | | | | | BMMC Ionomycin Hexos. | BMMC anti-IgE histamine | BMMC anti-IgE LTC4 | BMMC anti-IgE TNF-alpha | BMMC anti-IgE IL-6 | | |
| R935339 | 9999 | | | | | | | | | | | | | | | |
| R935340 | 3.606 | | | | | | | | | | | | | | | |
| R935351 | 9999 | 9999 | | | | | | | | | | | | | | |
| R935352 | | | | | | | | | | | | | | | | |
| R935353 | 9999 | 9999 | | | | | | | | | | | | | | |
| R935354 | 99 | 9999 | | | | | | | | | | | | | | |
| R935355 | 9999 | 9999 | | | | | | | | | | | | | | |
| R935356 | 99 | | | | | | | | | | | | | | | |
| R935357 | 99 | 9999 | | | | | | | | | | | | | | |
| R935358 | 9999 | 9999 | | | | | | | | | | | | | | |
| R935359 | 1.027 | 9999 | | | | | | | | | | | | | | |
| R935360 | 0.903 | 9999 | | | | | | | | | | | | | | |
| R935361 | 1.438 | 9999 | | | | | | | | | | | | | | |
| R935362 | 0.409 | 9999 | | | | | | | | | | | | | | |
| R935363 | 0.405 | 9999 | | | | | | | | | | | | | | |
| R935364 | 0.563 | 9999 | | | | | | | | | | | | | | |
| R935365 | 0.373 | 9999 | | | | | | | | | | | | | | |
| R935366 | 0.216 | 9999 | | | | | | | | | | | | | | |
| R935367 | 0.053 | 9999 | | | | | | | | | | | | | | |
| R940079 | 9999 | | | | | | | | | | | | | | | |
| R940110 | 9999 | 9999 | | | | | | | | | | | | | | |
| R940299 | 2.497 | 9999 | | | | | | | | | | | | | | |
| R940300 | 10 | 9999 | | | | | | | | | | | | | | |

TABLE 1

| TABLE 1 | | | | | | | | | | | | | | | | |
|------------------|------------------------------|-------------------------------|--------------------------|---------------------------|----------------------------|-----------------------------|------------------------------------|-------------------------------------|-------------------------------------|-----------------------------|-------------------------------|--------------------------|-------------------------------|--------------------------|--|--|
| Test Compound | Low Density | | | | CHMC anti-IgE Hexos. | CHMC ionomycin Hexos. | Basophils anti-IgE Histamine | Basophils ionomycin Histamine | Basophils Dust mite Histamine | High Density | | | | | | |
| | CHMC anti-IgE Tryptase | CHMC ionomycin Tryptase | CHMC anti-IgE LTC4 | BMMC anti-IgE hexos | | | | | | BMMC ionomycin Hexos. | BMMC anti-IgE histamine | BMMC anti-IgE LTC4 | BMMC anti-IgE TNF-alpha | BMMC anti-IgE IL-6 | | |
| | | | | | | | | | | | | | | | | |
| R940301 | 1.975 | 9999 | | | | | | | | | | | | | | |
| R940304 | 9999 | 9999 | | | | | | | | | | | | | | |
| R940306 | 1.1 | 9999 | | | | | | | | | | | | | | |
| R940307 | 0.291 | 9999 | | | | | | | | | | | | | | |
| R940308 | 0.612 | 4.168 | | | | | | | | | | | | | | |
| R940309 | 1.132 | 9999 | | | | | | | | | | | | | | |
| R940311 | 1.95 | | | | | | | | | | | | | | | |
| R940312 | 2.557 | | | | | | | | | | | | | | | |
| R940314 | 4.197 | | | | | | | | | | | | | | | |
| R940316 | 1.858 | | | | | | | | | | | | | | | |
| R940317 | 0.913 | 9999 | | | | | | | | | | | | | | |
| R940318 | 3.792 | | | | | | | | | | | | | | | |
| R940319 | 9999 | | | | | | | | | | | | | | | |
| R940321 | 9999 | | | | | | | | | | | | | | | |
| R940323 | 0.048 | 9999 | | | | | | | | | | | | | | |
| R940337 | 1.098 | | | | | | | | | | | | | | | |
| R940338 | 0.073 | 9999 | | | | | | | | | | | | | | |
| R921303 | 0.033 | 99 | | | | | | | | | | | | | | |
| R940345 | 1.712 | | | | | | | | | | | | | | | |
| R940346 | 0.142 | 99 | | | | | | | | | | | | | | |
| R940347 | 0.063 | 99 | | | | | | | | | | | | | | |
| R940348 | 2.189 | | | | | | | | | | | | | | | |
| R940349 | 0.044 | 7.4 | | | | | | | | | | | | | | |

TABLE 1

| Test Compound | Low Density | | | CHMC anti-IgE Hexos. | CHMC Ionomycin Hexos. | Basophils anti-IgE Histamine | Basophils Ionomycin Histamine | Basophils Dust mite Histamine | High Density | | | | | |
|---------------|------------------------|-------------------------|--------------------|----------------------|-----------------------|------------------------------|-------------------------------|-------------------------------|---------------------|-----------------------|-------------------------|--------------------|-------------------------|--------------------|
| | CHMC anti-IgE Tryptase | CHMC Ionomycin Tryptase | CHMC anti-IgE LTC4 | | | | | | BMMC anti-IgE hexos | BMMC Ionomycin Hexos. | BMMC anti-IgE histamine | BMMC anti-IgE LTC4 | BMMC anti-IgE TNF-alpha | BMMC anti-IgE IL-6 |
| R940350 | 0.092 | 4 | | | | | | | | | | | | |
| R940351 | 0.12 | 2.7 | | | | | | | | | | | | |
| R940352 | 0.101 | 9999 | | | | | | | | | | | | |
| R940353 | 0.091 | 9999 | | | | | | | | | | | | |
| R940354 | 0.115 | 99 | | | | | | | | | | | | |
| R945236 | 0.562 | 9999 | | | | | | | | | | | | |
| R945237 | 0.461 | 9999 | | | | | | | | | | | | |
| R945242 | 0.247 | 9999 | | | | | | | | | | | | |
| R945263 | 1.642 | | | | | | | | | | | | | |
| R921304 | 0.085 | 9999 | | | | | | | | | | | | |
| R945299 | | | | | | | | | | | | | | |
| R950244 | 9999 | | | | | | | | | | | | | |
| R950245 | 9999 | | | | | | | | | | | | | |
| R950246 | 9999 | | | | | | | | | | | | | |
| R950247 | 9999 | | | | | | | | | | | | | |
| R950261 | 0.611 | 9999 | | | | | | | | | | | | |
| R950262 | 0.285 | 9999 | | | | | | | | | | | | |
| R950263 | 0.284 | 3.299 | | | | | | | | | | | | |
| R950264 | 0.198 | 9999 | | | | | | | | | | | | |
| R950265 | 0.312 | 9999 | | | | | | | | | | | | |
| R950266 | 0.645 | 9999 | | | | | | | | | | | | |
| R950267 | 0.18 | 9999 | | | | | | | | | | | | |
| R950290 | 9999 | 9999 | | | | | | | | | | | | |

TABLE 1

| Test Compound | Low Density | | | CHMC anti-IgE Hexos. | CHMC ionomycin Hexos. | Basophils anti-IgE Histamine | Basophils ionomycin Histamine | Basophils Dust mite Histamine | High Density | | | | | |
|------------------|------------------------------|-------------------------------|--------------------------|----------------------------|-----------------------------|------------------------------------|-------------------------------------|-------------------------------------|---------------------------|-----------------------------|-------------------------------|--------------------------|-------------------------------|--------------------------|
| | CHMC anti-IgE Tryptase | CHMC ionomycin Tryptase | CHMC anti-IgE LTC4 | | | | | | BMMC anti-IgE hexos | BMMC ionomycin Hexos. | BMMC anti-IgE histamine | BMMC anti-IgE LTC4 | BMMC anti-IgE TNF-alpha | BMMC anti-IgE IL-6 |
| R950291 | 9999 | 9999 | | | | | | | | | | | | |
| R950293 | 3.689 | 8.155 | | | | | | | | | | | | |
| R950294 | 2.005 | 8.005 | | | | | | | | | | | | |
| R950295 | 2.041 | 8.795 | | | | | | | | | | | | |
| R950296 | 0.495 | 9999 | | | | | | | | | | | | |
| R950344 | 99 | | | | | | | | | | | | | |
| R950345 | 1.962 | 99 | | | | | | | | | | | | |
| R950346 | 0.345 | 9999 | | | | | | | | | | | | |
| R950347 | 0.548 | | | | | | | | | | | | | |
| R950348 | 0.066 | | | | | | | | | | | | | |
| R950349 | 0.078 | 9999 | | | | | | | | | | | | |
| R950356 | | | | | | | | | | | | | | |
| R950368 | 0.038 | 9999 | | | | | | | | | | | | |
| R950371 | | | | | | | | | | | | | | |
| R950372 | 1.348 | 9999 | | | | | | | | | | | | |
| R950373 | | | | | | | | | | | | | | |
| R950374 | 0.599 | 9999 | | | | | | | | | | | | |
| R950376 | 2.539 | | | | | | | | | | | | | |
| R950377 | 99 | | | | | | | | | | | | | |
| R950378 | | | | | | | | | | | | | | |
| R950379 | 0.545 | 9999 | | | | | | | | | | | | |
| R950380 | 3 | 9999 | | | | | | | | | | | | |
| R950381 | 0.11 | 99 | | | | | | | | | | | | |

TABLE 1

| TABLE 1 | | | | | | | | | | | | | | | | |
|------------------|------------------------------|-------------------------------|--------------------------|---------------------------|----------------------------|-----------------------------|------------------------------------|-------------------------------------|-------------------------------------|-----------------------------|-------------------------------|--------------------------|-------------------------------|--------------------------|--|--|
| Test Compound | Low Density | | | | CHMC anti-IgE Hexos. | CHMC ionomycin Hexos. | Basophils anti-IgE Histamine | Basophils ionomycin Histamine | Basophils Dust mite Histamine | High Density | | | | | | |
| | CHMC anti-IgE Tryptase | CHMC ionomycin Tryptase | CHMC anti-IgE LTC4 | BMMC anti-IgE hexos | | | | | | BMMC ionomycin Hexos. | BMMC anti-IgE histamine | BMMC anti-IgE LTC4 | BMMC anti-IgE TNF-alpha | BMMC anti-IgE IL-6 | | |
| | | | | | | | | | | | | | | | | |
| R950382 | | | | | | | | | | | | | | | | |
| R950383 | 0.114 | 9999 | | | | | | | | | | | | | | |
| R950385 | | | | | | | | | | | | | | | | |
| R950386 | 0.973 | | | | | | | | | | | | | | | |
| R950388 | 2.518 | | | | | | | | | | | | | | | |
| R950389 | 0.612 | 9999 | | | | | | | | | | | | | | |
| R950391 | 999 | 9999 | | | | | | | | | | | | | | |
| R950392 | 0.956 | 9999 | | | | | | | | | | | | | | |
| R950393 | 0.404 | 9999 | | | | | | | | | | | | | | |
| R945028 | | | | | | | | | | | | | | | | |
| R935241 | | | | | | | | | | | | | | | | |
| R940298 | | | | | | | | | | | | | | | | |
| R940302 | | | | | | | | | | | | | | | | |
| R940303 | | | | | | | | | | | | | | | | |
| R940305 | | | | | | | | | | | | | | | | |
| R935260 | 9999 | | | | | | | | | | | | | | | |
| R909258 | | | | | | | | | | | | | | | | |
| R940313 | 9999 | | | | | | | | | | | | | | | |
| R940315 | 9999 | | | | | | | | | | | | | | | |
| R935275 | 9999 | | | | | | | | | | | | | | | |
| R940320 | 9999 | | | | | | | | | | | | | | | |
| R940322 | 9999 | 9999 | | | | | | | | | | | | | | |
| R926910 | 9999 | 9999 | | | | | | | | | | | | | | |

TABLE 1

| Test Compound | Low Density | | | CHMC anti-IgE Hexos. | CHMC anti-IgE LTC4 | CHMC anti-IgE Hexos. | CHMC Ionomycin Hexos. | Basophils anti-IgE Histamine | Basophils Ionomycin Histamine | Basophils Dust mite Histamine | High Density | | | | | |
|---------------|------------------------|-------------------------|--------------------|----------------------|--------------------|----------------------|-----------------------|------------------------------|-------------------------------|-------------------------------|---------------------|-----------------------|-------------------------|--------------------|-------------------------|--------------------|
| | CHMC anti-IgE Tryptase | CHMC Ionomycin Tryptase | CHMC anti-IgE LTC4 | | | | | | | | BMMC anti-IgE hexos | BMMC Ionomycin Hexos. | BMMC anti-IgE histamine | BMMC anti-IgE LTC4 | BMMC anti-IgE TNF-alpha | BMMC anti-IgE IL-6 |
| R926911 | 9999 | 9999 | | | | | | | | | | | | | | |
| R926912 | 9999 | 9999 | | | | | | | | | | | | | | |
| R926853 | 9999 | 9999 | | | | | | | | | | | | | | |
| R926852 | 9999 | 9999 | | | | | | | | | | | | | | |
| R926854 | 9999 | 9999 | | | | | | | | | | | | | | |
| R926920 | 9999 | 9999 | | | | | | | | | | | | | | |
| R926921 | 99 | 9999 | | | | | | | | | | | | | | |
| R926924 | 99 | 9999 | | | | | | | | | | | | | | |
| R926858 | | | | | | | | | | | | | | | | |
| R926861 | 9999 | 9999 | | | | | | | | | | | | | | |
| R945298 | 9999 | 9999 | | | | | | | | | | | | | | |
| R940328 | 9999 | | | | | | | | | | | | | | | |
| R926869 | | | | | | | | | | | | | | | | |
| R926873 | 9999 | | | | | | | | | | | | | | | |
| R926875 | 9999 | | | | | | | | | | | | | | | |
| R926876 | 9999 | | | | | | | | | | | | | | | |
| R926877 | 9999 | | | | | | | | | | | | | | | |
| R940336 | 9999 | | | | | | | | | | | | | | | |
| R926878 | 9999 | | | | | | | | | | | | | | | |
| R926882 | 9999 | | | | | | | | | | | | | | | |
| R926884 | 9999 | | | | | | | | | | | | | | | |
| R926889 | 9999 | | | | | | | | | | | | | | | |
| R920400 | 9999 | | | | | | | | | | | | | | | |

TABLE 1

| Test Compound | Low Density | | | CHMC anti-IgE Tryptase | CHMC ionomycin Tryptase | CHMC anti-IgE LTC4 | CHMC anti-IgE Hexos. | CHMC ionomycin Hexos. | Basophils anti-IgE Histamine | Basophils ionomycin Histamine | Basophils Dust mite Histamine | High Density | | | | | |
|------------------|------------------------------|-------------------------------|--------------------------|------------------------------|-------------------------------|--------------------------|----------------------------|-----------------------------|------------------------------------|-------------------------------------|-------------------------------------|---------------------------|-----------------------------|-------------------------------|--------------------------|-------------------------------|--------------------------|
| | CHMC anti-IgE Tryptase | CHMC ionomycin Tryptase | CHMC anti-IgE LTC4 | | | | | | | | | BMMC anti-IgE hexos | BMMC ionomycin Hexos. | BMMC anti-IgE histamine | BMMC anti-IgE LTC4 | BMMC anti-IgE TNF-alpha | BMMC anti-IgE IL-6 |
| R920401 | 9999 | | | | | | | | | | | | | | | | |
| R920402 | 9999 | | | | | | | | | | | | | | | | |
| R920403 | 9999 | | | | | | | | | | | | | | | | |
| R940342 | 99 | | | | | | | | | | | | | | | | |
| R920409 | 9999 | | | | | | | | | | | | | | | | |
| R940344 | 9999 | | | | | | | | | | | | | | | | |
| R926888 | 9999 | | | | | | | | | | | | | | | | |
| R926758 | | | | | | | | | | | | | | | | | |
| R927024 | 0.326 | 99 | | | | | | | | | | | | | | | |
| R927025 | 0.326 | | | | | | | | | | | | | | | | |
| R927026 | 9999 | 9999 | | | | | | | | | | | | | | | |
| R927027 | 9999 | 9999 | | | | | | | | | | | | | | | |
| R927028 | 0.208 | 9999 | | | | | | | | | | | | | | | |
| R927029 | | | | | | | | | | | | | | | | | |
| R927030 | 0.26 | 9999 | | | | | | | | | | | | | | | |
| R927031 | 0.215 | 99 | | | | | | | | | | | | | | | |
| R927032 | 0.899 | | | | | | | | | | | | | | | | |
| R927035 | 0.583 | 9999 | | | | | | | | | | | | | | | |
| R927036 | | | | | | | | | | | | | | | | | |
| R927037 | 0.233 | 9999 | | | | | | | | | | | | | | | |
| R927038 | 1.05 | 9999 | | | | | | | | | | | | | | | |
| R927039 | 1.23 | 9999 | | | | | | | | | | | | | | | |
| R927040 | 1.05 | 9999 | | | | | | | | | | | | | | | |

TABLE 1

| TABLE 1 | | | | | | | | | | | | | | | |
|------------------|------------------------------|-------------------------------|--------------------------|---------------------------|----------------------------|-----------------------------|------------------------------------|-------------------------------------|-------------------------------------|-----------------------------|-------------------------------|--------------------------|-------------------------------|--------------------------|--|
| Test Compound | Low Density | | | | CHMC anti-IgE Hexos. | CHMC Ionomycin Hexos. | Basophils anti-IgE Histamine | Basophils Ionomycin Histamine | Basophils Dust mite Histamine | High Density | | | | | |
| | CHMC anti-IgE Tryptase | CHMC Ionomycin Tryptase | CHMC anti-IgE LTC4 | BMMC anti-IgE hexos | | | | | | BMMC Ionomycin Hexos. | BMMC anti-IgE histamine | BMMC anti-IgE LTC4 | BMMC anti-IgE TNF-alpha | BMMC anti-IgE IL-6 | |
| | | | | | | | | | | | | | | | |
| R927041 | 0.788 | 9999 | | | | | | | | | | | | | |
| R927042 | | | | | | | | | | | | | | | |
| R935270 | | | | | | | | | | | | | | | |
| R935368 | 0.082 | 9999 | | | | | | | | | | | | | |
| R935369 | 0.255 | 9999 | | | | | | | | | | | | | |
| R935370 | | | | | | | | | | | | | | | |
| R935371 | 0.794 | 9999 | | | | | | | | | | | | | |
| R935372 | 0.06 | 9999 | | | | | | | | | | | | | |
| R935373 | 0.274 | 9999 | | | | | | | | | | | | | |
| R935374 | 0.356 | 9999 | | | | | | | | | | | | | |
| R935375 | 10 | 9999 | | | | | | | | | | | | | |
| R935376 | | | | | | | | | | | | | | | |
| R935377 | | | | | | | | | | | | | | | |
| R935378 | 0.566 | 9999 | | | | | | | | | | | | | |
| R935379 | | | | | | | | | | | | | | | |
| R935380 | 1.61 | 99 | | | | | | | | | | | | | |

TABLE 2

| TABLE 2 | | | | | | | | | | | | | | |
|---------|-------------------------------|----------------------------------|-----------------------------------|------------------------------|-----------------------------------|-------------------------------|-----------------------------------|--------------------------------------|---------------------------------|------------------------------------|--|--|--|--|
| | High Density | | | | | | Toxicity Jurkat Light Scat. | Toxicity Jurkat Cell Titer Glo | Toxicity BJAB Light Scat. | Toxicity BJAB Cell Titer Glo | | | | |
| | CHMC high density hexos | CHMC high density tryptase | CHMC high density histamine | CHMC high density LTC4 | CHMC high density TNF-alpha | CHMC high density IL-13 | | | | | | | | |
| R008951 | | | | | | | | | | | | | | |
| R008952 | | | | | | | | | | | | | | |
| R008953 | | | | | | | | | | | | | | |
| R008955 | | | | | | | | | | | | | | |
| R008956 | | | | | | | | | | | | | | |
| R008958 | | | | | | | | | | | | | | |
| R067934 | | | | | | | | | | | | | | |
| R067963 | | | | | | | | | | | | | | |
| R070153 | | | | | | | | | | | | | | |
| R070791 | | | | | | | | | | | | | | |
| R081166 | | | | | | | | | | | | | | |
| R088814 | | | | | | | | | | | | | | |
| R088815 | | | | | | | | | | | | | | |
| R091880 | | | | | | | | | | | | | | |
| R092788 | | | | | | | 9999 | | 9999 | | | | | |
| R909241 | | | | | | | | 3.736 | | | | | | |
| R921219 | 0.124 | 0.121 | 0.162 | 0.034 | 0.190 | 0.175 | | >10 | | >10 | | | | |
| R925775 | | | | | | | 9999 | | 9999 | | | | | |
| R925778 | | | | | | | 9999 | | 9999 | | | | | |
| R925779 | | | | | | | >10 | | 9999 | | | | | |
| R925797 | | | | | | | >10 | | 9999 | | | | | |
| R926108 | | | | | | | >10 | | >10 | | | | | |
| R926109 | 0.783 | 0.906 | 1.827 | 0.808 | 1.504 | 1.664 | >10 | | 9999 | | | | | |

TABLE 2

| TABLE 2 | | | | | | | | | | | |
|---------|-------------------------------|----------------------------------|-----------------------------------|------------------------------|-----------------------------------|-------------------------------|-----------------------------------|--------------------------------------|---------------------------------|------------------------------------|--|
| | High Density | | | | | | Toxicity Jurkat Light Scat. | Toxicity Jurkat Cell Titer Glo | Toxicity BJAB Light Scat. | Toxicity BJAB Cell Titer Glo | |
| | CHMC high density hexos | CHMC high density tryptase | CHMC high density histamine | CHMC high density LTC4 | CHMC high density TNF-alpha | CHMC high density IL-13 | | | | | |
| R926110 | | | | | | | >10 | | >10 | | |
| R921218 | 0.464 | 0.647 | 0.463 | 0.695 | 1.752 | 2.0776 | >10 | | >10 | | |
| R926113 | 1.448 | 1.649 | 1.848 | 0.468 | 5.678 | 3.569 | >10 | | >10 | | |
| R926146 | | | | | | | 9999 | | 9999 | | |
| R926210 | | | | | | | >10 | | 9999 | | |
| R926240 | | | | | | | 10 | | 9999 | | |
| R926248 | | | | | | | >10 | | 9999 | | |
| R926249 | | | | | | | >10 | | 9999 | | |
| R926253 | | | | | | | 9999 | | 9999 | | |
| R926256 | | | | | | | >10 | | 9999 | | |
| R926258 | | | | | | | 9999 | | 9999 | | |
| R926387 | | | | | | | >10 | | 9999 | | |
| R926395 | | | | | | | >10 | | 9999 | | |
| R926396 | | | | | | | >10 | | 9999 | | |
| R926411 | | | | | | | 8.5 | | >10 | | |
| R926486 | 1.088 | 1.313 | 1.928 | 0.834 | 0.455 | | | | | | |
| R926488 | 0.521 | 0.623 | 0.792 | 0.201 | 2.443 | 1.012 | | | | | |
| R926493 | 0.889 | 1.093 | 1.324 | 0.474 | >2 | | | >4.33 | | | |
| R926494 | 0.640 | >2 | 9999 | 0.326 | 9999 | | | | | | |
| R926495 | 0.100 | 0.235 | 0.066 | 0.241 | 0.362 | 0.449 | | >10 | | >10 | |
| R926496 | 0.429 | 0.533 | 0.809 | 0.414 | 0.622 | | | | | | |
| R926497 | 1.106 | 1.234 | 1.333 | | 1.876 | 9999 | | | | | |
| R926501 | >2 | >2 | 9999 | | 9999 | 9999 | | >4.33 | | >4.33 | |

TABLE 2

| TABLE 2 | | | | | | | | | | | |
|---------|-------------------------------|----------------------------------|-----------------------------------|------------------------------|-----------------------------------|-------------------------------|-----------------------------------|--------------------------------------|---------------------------------|------------------------------------|--|
| | High Density | | | | | | Toxicity Jurkat Light Scat. | Toxicity Jurkat Cell Titer Glo | Toxicity BJAB Light Scat. | Toxicity BJAB Cell Titer Glo | |
| | CHMC high density hexos | CHMC high density tryptase | CHMC high density histamine | CHMC high density LTC4 | CHMC high density TNF-alpha | CHMC high density IL-13 | | | | | |
| R926502 | >2 | >2 | >2 | | 1.807 | >2 | | 1.513 | | | |
| R926505 | | | | | | | | 4.199 | | | |
| R926508 | 0.170 | 0.434 | 0.105 | | 0.505 | 0.763 | | >10 | | >10 | |
| R926510 | 0.921 | 1.115 | 1.667 | | 0.417 | 0.886 | | 2.77 | | | |
| R926511 | 1.183 | 1.474 | 1.73 | | 1.307 | >2 | | >4.33 | | >4.33 | |
| R926614 | >10 | >10 | | | >10 | 6.442 | | | | | |
| R926696 | <1.1 | <1.1 | <1.1 | <1.1 | <1.1 | 1.773 | | >5.0 | | | |
| R926699 | <1.1 | <1.1 | 1.44 | <1.1 | <1.1 | 1.294 | | | | | |
| R926700 | <1.1 | <1.1 | <1.1 | <1.1 | <1.1 | 2.053 | | | | | |
| R926703 | 1.512 | 1.947 | >2 | 0.724 | >2 | | | | | | |
| R926704 | >2 | 9999 | 9999 | 9999 | 9999 | | | | | | |
| R926705 | 1.007 | 1.256 | 0.641 | 0.494 | 9999 | | | | | | |
| R926706 | >2 | 9999 | 9999 | 1.491 | 9999 | | | | | | |
| R926742 | 0.104 | 0.217 | 0.080 | | 0.385 | 0.667 | | 9 | | >10 | |
| R926745 | | | | | | | | >10 | | >10 | |
| R926780 | | | | | | | | >5.0 | | | |
| R926782 | | | | | | | | >4.33 | | >4.33 | |
| R935075 | 0.647 | 1.212 | 0.443 | <0.22 | >2 | | | >4.33 | | >4.33 | |
| R935154 | | | | | | | | >4.33 | | | |
| R935156 | | | | | | | | 4.054 | | | |
| R940216 | <1.1 | <1.1 | 1.176 | <1.1 | 3.188 | 3.006 | | | | | |
| R940233 | 0.577 | 0.642 | 0.586 | 0.118 | 2.247 | 1.781 | | >4.33 | | >4.33 | |
| R945032 | 0.357 | 0.458 | 0.439 | 0.0929 | 1.082 | 0.291 | | | | | |

TABLE 2

| TABLE 2 | | | | | | | | | | |
|---------|-------------------------------|----------------------------------|-----------------------------------|------------------------------|-----------------------------------|-------------------------------|-----------------------------------|--------------------------------------|---------------------------------|------------------------------------|
| | High Density | | | | | | Toxicity Jurkat Light Scat. | Toxicity Jurkat Cell Titer Glo | Toxicity BJAB Light Scat. | Toxicity BJAB Cell Titer Glo |
| | CHMC high density hexos | CHMC high density tryptase | CHMC high density histamine | CHMC high density LTC4 | CHMC high density TNF-alpha | CHMC high density IL-13 | | | | |
| R945033 | 8.151 | 8.868 | | | >10 | 5.983 | | | | |
| R945071 | <1.1 | <1.1 | <1.1 | <1.1 | <1.1 | <1.1 | | | | |
| R945128 | 1.279 | 1.749 | 0.547 | 0.729 | >2 | ND | | | | |
| R945140 | 0.994 | 1.112 | 1.551 | | 1.714 | 9999 | | | | |
| R945142 | >2 | >2 | 9999 | | >2 | 9999 | | | | |
| R945150 | | | | | | | | >4.33 | | >4.33 |
| R921302 | 0.682 | 0.795 | 1.588 | 0.514 | 1.173 | 1.672 | | | | |
| R950141 | 0.567 | 0.618 | 0.627 | 0.201 | 1.059 | 0.798 | | | | |
| R950207 | | | | | | | | >4.33 | | |

7.7 The 2,4-Pyrimidinediamine Compounds of the Invention Selectively Inhibit the Upstream IgE Receptor Cascade

To confirm that many of the 2,4-pyrimidinediamine compounds of the invention exert their inhibitory activity by blocking or inhibiting the early IgE receptor signal transduction cascade, several of the compounds were tested in cellular assays for ionomycin-induced degranulation, as described below.

7.7.1 CHMC Low Cell Density Ionomycin Activation: Tryptase Assay

Assays for ionomycin-induced mast cell degranulation were carried out as described for the CHMC Low Density IgE Activation assays (Section 6.4.3, *supra*), with the exception that during the 1 hour incubation, 6X ionomycin solution [5mM ionomycin (Sigma I-0634) in MeOH (stock) diluted 1:416.7 in MT buffer (2 μ M final)] was prepared and cells were stimulated by adding 25 μ l of the 6X ionomycin solution to the appropriate plates.

7.7.2 Basophil Ionomycin Activation: Histamine Release Assay

Assays for ionomycin-induced basophil cell degranulation were carried out as described for the Basophil IgE or Dustmite Activation Assay (Section 6.4.6, *supra*), with the exception that following incubation with compound, cells were stimulated with 20 μ l of 2 μ M ionomycin.

7.7.3 Results

The results of the ionomycin-induced degranulation assays, reported as IC₅₀ values (in μ M) are provided in TABLE 1, *supra*. Of the active compounds tested (*i.e.*, those that inhibit IgE-induced degranulation), the vast majority do not inhibit ionomycin-induced degranulation, confirming that these active compounds selectively inhibit the early (or upstream) IgE receptor signal transduction cascade.

These results were confirmed for certain compounds by measuring anti-IgE-induced and ionomycin-induced calcium ion flux in CHMC cells. In these Ca²⁺ flux tests, 10 μ M R921218 and 10 μ M R902420 inhibited anti-IgE-induced Ca²⁺ flux, but had no effect on ionomycin-induced Ca²⁺ flux (See FIG. 4).

7.8 The Inhibitory Effect of the 2,4-Pyrimidinediamine Compounds of the Invention is Immediate

To test the immediacy of their inhibitory effect, certain 2,4-pyrimidinediamines of the invention were added simultaneously with anti-IgE antibody activator in the cellular assays described above. All compounds tested blocked IgE-induced degranulation of CHMC cells to the same extent as observed when the compounds were pre-incubated with CHMC cells for 10 or 30 min. prior to receptor cross-linking.

7.9 Kinetics of Pharmacological Activity *In vitro*

Compounds R921218, R921302, R921219, R926240, R940277, R926742, R926495, R909243 and R926782 were tested in washout experiments. In the experiments, CHMC cells were either activated immediately with anti-IgE antibody in the presence of 1.25 μ M compound (time zero), or the compound was washed out followed by activation with anti-IgE antibody at 30, 60 or 120 min. The inhibitory activity of these compounds was greatly diminished 30 min. after compound removal, indicating that constant exposure of mast cells to these compounds is required for maximal inhibition of degranulation. The other compounds tested yielded similar results.

7.10 Toxicity: T- and B-Cells

The ability of the compounds of the invention to exert their inhibitory activity without being toxic to cells of the immune system was demonstrated in cellular assays with B- and T-cells. The protocols for the assays are provided below.

7.10.1 Jurkat (T-Cell) Toxicity

Dilute Jurkat cells to 2×10^5 cells/ml in complete RPMI (10% heat-inactivated fetal bovine serum) media and incubate at 37°C, 5% CO₂ for 18 hours. Add 65 μ l cells at 7.7×10^5 cells/ml to a 96-well V-bottom plate (TC-treated, Costar) containing 65 μ l 2X compound (final vehicle concentration is 0.5% DMSO, 1.5% MeOH). Mix, incubate plates for 18-24 hr at 37°C, 5% CO₂. Toxicity was assessed by flow cytometric analysis of cellular light scatter

7.10.2 BJAB (B-Cell) Toxicity

The B-cell line BJAB was cultured in log phase in RPMI1640 + 10% heat-inactivated fetal bovine serum, 1x L-glutamine, 1x penicillin, 1x streptavidin and 1x beta-

mercaptoethanol at 37°C, 5% CO₂. First, BJABs were harvested, spun and resuspended in culture medium to a concentration of 7.7×10^5 cells/mL. 65uL cells were mixed with 65 uL compound, in duplicate and in the presence of 0.1% DMSO in a V-bottomed 96-well tissue culture plate. Cells were incubated with compound at various dilutions at 37°C, 5% CO₂.

5 Toxicity was assessed by flow cytometric analysis of cellular light scatter.

7.10.3 Toxicity: Cell Titer Glo Assay

Seed 50 µl cells (1×10^6 /ml) into each well containing 50 µl compound. The final vehicle concentration is 0.5% DMSO, 1.5% MeOH. Shake plates for 1 minute to mix cells and compound. Incubate plates at 37°C (5% CO₂) for 18 hours. Next day, harvest 50
10 µl cells from each well, add to 50 µl Cell Titer Glo reagent (Invitrogen). Shake plates for 1 minute. Read on luminometer.

7.10.4 Results

The results of the T- and B-cell toxicity assays, reported as IC₅₀ values (in µM), are presented in TABLE 2, *supra*. With a few exceptions (see TABLE 1), all
15 compounds tested were non-toxic to both B- and T-cells at effective inhibitory concentrations. Assays performed with primary B-cells yielded similar results.

7.11 The 2,4-Pyrimidine Compounds Are Tolerated In Animals

The ability of the compounds of the invention to exert their inhibitory activity at doses below those exhibiting toxicity in animals was demonstrated with compounds
20 R921218, R921219 and R921302.

7.11.1 R921218

R921218 was studied in an extensive program of non-clinical safety studies that concluded this agent to be well tolerated in both rodents and non-rodents. To summarize the outcome of toxicology/non-clinical safety testing with R921218; this agent
25 produced no dose limiting toxicity by the intranasal route of administration in non-rodents (rabbits and primates) or by the oral route of administration in rodents (mice and rats) during 14-day repeat-dose toxicity studies at doses many fold above the anticipated dose expected to produce efficacy in man. There were no adverse findings in a core safety pharmacology battery of cardiovascular, respiratory and/or central nervous system function.
30 There was no evidence for mutagenic or clastogenic potential in genetic toxicology testing

nor were there untoward effects after exposure to skin and eyes. A short discussion of key toxicology studies is provided.

A 14-day repeat-dose intranasal toxicity study in *Cynomolgus* monkeys was performed at doses of 2.1, 4.5 or 6.3 mg/kg/day. In life parameters included: clinical observations, body weights, food consumption, ophthalmology, blood pressure, electrocardiography, hematology, clinical chemistry, urinalysis, immunotoxicological assessment, gross necropsy, organ weights, toxicokinetic assessments and histopathology (including the nasal cavity). There were no adverse findings attributed to R921218 in any study parameter and the NOAEL (no observed adverse effect level) was considered 6.3 mg/kg/day.

A 14-day repeat-dose intranasal toxicity study in New Zealand White rabbits was performed at doses of 1.7, 3.4 or 5.0 mg/kg/day. In life parameters included: clinical observations, body weights, food consumption, ophthalmology, hematology, clinical chemistry, gross necropsy, organ weights, toxicokinetic assessments and histopathology (including the nasal cavity). There were no adverse findings attributed to R921218 in any study parameter and the NOAEL (no observed adverse effect level) was considered 5.0 mg/kg/day.

7.11.2 R921219

In pilot dose finding studies a single dose oral dose of 600 mg/kg was considered a NOEL (no observed effect level) while multiple (7-day) doses of 200 mg/kg/day and above were not tolerated.

In the *in vitro* *Salmonella-Escherichia coli*/Mammalian-Microsome Reverse Mutation Assay (Ames test), R921219 was found to test positive in tester strain TA1537, with and without metabolic activation, confirming the results of an earlier study. R921219 was not found to adversely affect any of the other 4 tester strains. R921219 was not found to possess clastogenic potential when studied in an *in vitro* chromosomal aberration assay.

7.11.3 R921302

Several non-GLP pilot toxicity studies have been conducted in rodents. In the mouse an oral dose of 1000 mg/kg was tolerated for up to 7-days. In a 14-day oral toxicity study in the mouse was conducted with doses of 100, 300 and 1000 mg/kg. A dose of 1000 mg/kg was not tolerated, while a dose of 300 mg/kg promoted evidence for

histopathological changes in the vulva. A dose of 100 mg/kg was considered the NOAEL (no observed adverse effect level) in the study. A 28-day oral toxicity study in the mouse was conducted at doses of 100 mg/kg q.d., 100 mg/kg b.i.d., 300 mg/kg q.d. and 300 mg/kg b.i.d. R921302 was not tolerated at 300 mg/kg q.d. or b.i.d. The lower doses (100 mg/kg q.d. or b.i.d.) appeared to be well tolerated (results of clinical and histopathology are not yet known). In the rat oral doses of 50, 150 and 300 mg/kg given for 32 days appeared to be well tolerated (results of clinical and histopathology are not yet known).

In the *in vitro* *Salmonella-Escherichia coli*/Mammalian-Microsome Reverse Mutation Assay (Ames test), R921302 was found to test positive in tester strain TA98 with S9 and TA1537, with and without metabolic activation. R921302 was not found to adversely affect any of the other 3 tester strains. R921302 was not clastogenic when assessed in an *in vitro* chromosomal aberration assay.

7.12 The 2,4-Pyrimidinediamine Compounds Are Orally Bioavailable

Over 50 2,4-pyrimidinediamine compounds of the invention were tested for oral bioavailability. For the study, compounds were dissolved in various vehicles (e.g. PEG 400 solution and CMC suspension) for intravenous and oral dosing in the rats. Following administration of the drug, plasma samples were obtained and extracted. The plasma concentrations of the compounds were determined by high performance liquid chromatography/tandem mass spectrometry (LC/MS/MS) methods. Pharmacokinetic analyses were performed based on the plasma concentration data. The pharmacokinetic parameters of interest include Clearance (CL), Volume of distribution at steady-state (V_{ss}), terminal half-life (t_{1/2}), and oral bioavailability (%F).

These pharmacokinetic studies indicate that many of the 2,4-pyrimidinediamine compounds are orally available, with %F up to approximately 50% (in the range of 0-50%). The half-lives ranged from 0.5 to 3 hr. In particular, Compounds R940350, R935372, R935193, R927050 and R935391 exhibited good oral bioavailabilities and half-lives in rats. Thus, these studies confirm that these 2,4-pyrimidinediamine compounds are suitable for oral administration.

7.13 The Compounds Are Effective for the Treatment of Allergies

The *in vivo* efficacy of compounds R926109, R921218, R921219, R921302, R926495, R926508, R926742, R926745 and R945150 towards allergies was evaluated in

the mouse model of passive cutaneous anaphylaxis (PCA). This model provides a direct measure of IgE-induced degranulation of tissue mast cells. In this model, IgE primed animals are exposed to an allergen challenge, and the change in permeability of dermal vasculature that results from histamine release from mast cells is measured by change in the amount of dye leakage into surrounding tissue. Inhibition of mediator release by compounds that modulate mast cell degranulation is easily measured by extracting the dye from the tissue.

7.13.1 Study Protocol and Results

In the PCA assay mice are passively sensitized by intradermal injection with anti-dinitrophenol (DNP) IgE antibodies (Day -1). At predetermined times animals are treated with the test agent (Day 0). The modulatory effect of the agent on cutaneous mast cell degranulation is measured following intravenous injection of DNP conjugated to human serum albumin (HSA-DNP), together with Evans blue dye. The resulting cross-linking of the IgE receptor and subsequent mast cell degranulation-induced increase in vascular permeability is determined by measuring the amount of dye extravasation into the tissue. Dye is extracted from the tissue by formamide, and the absorbance of this extract is read at 620 nm. The inhibitory effect of drug treatment is reported as the percent inhibition compared to vehicle treatment, that is, the percent reduction in A_{620} .

Two compounds have been tested as positive controls: the histamine antagonist diphenhydramine and the serotonin antagonist cyproheptadine. Both mediators (histamine and serotonin) are released upon IgE-mediated degranulation from the mouse mast cell. Both reference compounds inhibit the PCA response; cyproheptadine was used routinely in subsequent experiments. Cyproheptadine reproducibly inhibited the PCA response by 61% +/- 4% (8 mg/kg, i.p., 30 minutes pretreatment time, n=23 experiments).

7.13.1.1 Results

A dose-dependent inhibition of the FcεR--mediated vascular leakage was observed with increasing doses of R921218, R926109, R921219 and RR921302. These compounds were administered either in a solution formulation (67%PEG/33% citrate buffer) or an aqueous suspension (1.5% Avicel). These results demonstrate the strong correlation between compound plasma levels, in vivo efficacy, and *in vitro* potency. The most potent compound, R921219, was active with circulating exposure levels of

approximately 10 $\mu\text{g/ml}$ (68% inhibition at a dose level of 100 mg/kg) compared with R921302, a relatively less potent molecule, which reduced plasma extravasation by 42% at a dose level of 100 mg/kg. Further, the length of exposure to circulating compound was reflected in the duration of inhibitory activity. R921302, determined to be the most
5 metabolically stable compound in pharmacokinetics studie, inhibited the vascular permeability for 1-2 hours prior to antigen-induced receptor signaling, where after the efficacy began to decrease. These data are summarized in TABLE 3 and TABLE 4.

| TABLE 3 | | | | | | |
|--|-------|---------------------------|-------------------------|--------------|--------------|----------------------|
| Efficacy of R921218, R926109, R921219 and R921302 in the PCA Assay | | | | | | |
| Compound | Route | Vehicle | Pretreatment time (min) | Dose (mg/kg) | % Inhibition | Plasma level (µg/ml) |
| R921218 | PO | 67%PEG/33% citrate buffer | 10 | 50 | 7 | 3 |
| | | | | 100 | 11 | 4 |
| | | | | 200 | 50 | 18 |
| R926109 | PO | 67%PEG/33% citrate buffer | 15 | 50 | 22 | N.D. |
| | | | | 100 | 32 | |
| | | | | 200 | 48 | |
| R921219 | PO | 1.5% Avicel/water | 15 | 30 | 25 | 0.4 |
| | | | | 100 | 68 | 4 |
| | | | | 300 | 92 | 11 |
| R921302 | PO | 1.5% Avicel/water | 60 | 50 | 35 | 25 |
| | | | | 100 | 42 | 38 |
| | | | | 150 | 56 | 64 |
| | | | | 200 | 93 | 105 |

| TABLE 4 | | | | | | |
|--|-------|-------------------|--------------|-------------------------|--------------|----------------------|
| Duration of action of R921219 and R921302 in the PCA Assay | | | | | | |
| Compound | Route | Vehicle | Dose (mg/kg) | Pretreatment time (min) | % Inhibition | Plasma level (µg/ml) |
| RR921302 | PO | 1.5% Avicel/water | 200 | 30 | 89 | 88 |
| | | | | 60 | 83 | 53 |
| | | | | 120 | 82 | 61 |
| | | | | 240 | 37 | 8 |

Similar in vivo activity was observed with compounds R926495, R926508, R926742,

5. R926745 and R926150, which were able to inhibit the PCA response after administration by the oral route in a PEG-based formulation (data not shown).

7.14 The Compounds Are Effective in the Treatment of Asthma

The efficacy of compounds R921218, R921302, R926495, R926508, R926742 and R921219 in the treatment of asthma was demonstrated in the sheep model of allergic asthma. Sheep develop bronchoconstriction within minutes of exposure to inhaled antigen (Ascaris suum), with maximal airflow obstruction during the early allergic response (EAR). Release of preformed mast cell mediators is likely responsible for this early phase of airflow obstruction. In addition to the EAR, the sheep model allows us to evaluate the effect of our compounds on the late asthmatic reaction (LAR) and non-specific airway hyperresponsiveness (AHR), which occur as a result of topical or local administration of allergen to the airway. In the sheep, AHR develops a few hours following antigen challenge, and can persist for up to 2 weeks. The results described below demonstrate the potential of the tested compounds to inhibit a cascade of events that may be a result of release of cytokines from the mast cell.

7.14.1 Study Protocol

In the sheep model of allergic asthma, sheep are administered aerosols of test article *via* an endotracheal tube, followed by an aerosol challenge with antigen extracted from the roundworm, *Ascaris suum*, to which the sheep are naturally allergic. Allergen challenge leads to direct bronchoconstriction (both EAR and LAR) and a persistent non-specific AHR. These three characteristics are similar to those seen in human allergic asthmatics. The activity of the test agent is determined by changes in the lung resistance (R_L), which is calculated from measurements of transpulmonary pressure, flow, and respiratory volume. The historical control data obtained from the same sheep following saline treatment compared with an allergen challenge show that a sharp increase of R_L occurs during the EAR and persists for approximately 2-3 hours following allergen challenge. The LAR is a less pronounced increase in R_L , which starts approximately 5-6 hours following allergen challenge and is resolved by 8 hours post-challenge. Twenty-four hours after the challenge, a dose response to carbachol is measured to determine the AHR, which is expressed as the dose of carbachol required to increase R_L by 400% over baseline. (This measurement is referred to as the provocative concentration of carbachol that elicits a 400% increase in R_L over baseline (PC_{400})). The data are compared to historical control data for the same individual when administered a saline control aerosol and challenged with *Ascaris suum*.

7.14.2 Result

All the compounds tested showed inhibitory effects in the LAR and the AHR, and several of these agents inhibited the EAR as well. The optimal response for each compound in a series of studies to evaluate activity at several pretreatment times and using several different solution and suspension formulations are shown in TABLE 5. The efficacy of R921218 on the EAR appeared to be dependent on the formulation, with the greatest effect seen at 30 mg/sheep administered as a solution aerosol in 10% ethanol. R926495, R926742, R926508 and R921219, administered in four different sheep at 45 mg/sheep in an aqueous suspension 60 minutes prior to allergen challenge, demonstrate that the LAR and AHR is blocked. In addition to these late parameters, the EAR was greatly reduced by treatment with R921219, R926508 or R926495. The efficacy of RR921302 was investigated using a 45%PEG400/55% citrate buffer vehicle. Under these conditions, R921302, administered at 30 mg/sheep 60 minutes prior to challenge, blocked the LAR and AHR, and EAR was unaffected.

These data clearly demonstrate that these compounds are able to block the asthmatic responses in allergic sheep. All compounds inhibited the AHR and LAR significantly when compared to the historical control. The EAR was significantly inhibited by R921219, R926508 and R926495 (54%, 21% and 33% respectively). In contrast, R921218, R921302 and R926742 failed to inhibit the EAR when administered in an aqueous suspension.

TABLE 5
Efficacy Of Exemplary Compounds In A Sheep Model Of Allergic Asthma

| Compound | Dose (mg/sheep) | Pretreatment time (min) | Vehicle | EAR (%) inhibition | LAR (%) inhibition | AHR (%) inhibition |
|----------|--------------------|----------------------------|---------------------------------|-----------------------|-----------------------|-----------------------|
| R921218 | 30 | 15 | 10% ethanol | 66 | 78 | 101 |
| R926742 | 45 | 60 | Aqueous suspension | -19 | 87 | 94 |
| R926495 | 45 | 60 | | 33 | 85 | 41 |
| R926508 | 45 | 60 | | 21 | 90 | 88 |
| R921219 | 45 | 60 | | 56 | 75 | 90 |
| RR921302 | 30 | 60 | 45%PEG400/55% citrate buffer | -28 | 86 | 82 |

7.15 The Compounds Are Effective In The Treatment of Asthma

The efficacy of compounds R921304 and R921219 in the treatment of asthma was also demonstrated in a mouse model of allergic asthma.

7.15.1 Study protocol

5 Mice are sensitized to ovalbumin (chicken protein) in the presence of an adjuvant (Alum) by the intraperitoneal route on day 0 and day 7. One week later, mice are challenged intranasally with ovalbumin on Days 14, 15 and 16 (more stringent model) or on Day 14 (less stringent model). This sensitization and challenge regimen leads to airway hyperresponsiveness and inflammation in the lungs, which are two dominant characteristics
10 of human allergic asthma. In the mouse model, the in vivo airway responses are measured using a whole body plethysmograph which determines the PENH (enhanced Pause, Buxco Electronics). The PENH is a dimensionless value comprised of the peak inspiratory flow (PIF), peak expiratory flow (PEF), time of inspiration, time of expiration and relaxation time, and is considered a validated parameter of airway responsiveness. Responses to
15 allergen challenge (OVA) are compared with animals challenged with saline only. Twenty-four hours after challenge, mice are exposed to increasing doses of methacholine (muscarinic receptor agonist) which results in smooth muscle contraction. The ovalbumin-challenged mice demonstrate a significant airway hyperresponsiveness to methacholine when compared to the saline challenged mice. In addition, a cellular infiltrate in the airway
20 is observed in ovalbumin challenged mice when compared with the saline challenged mice. This cellular infiltrate is mainly characterized by eosinophils, but a smaller influx of neutrophils and mononuclear cells is also present.

The use of this model for the evaluation of small molecule inhibitors of mast cell degranulation has been validated in several ways. First, using mast cell deficient mice
25 (W/W^v) it has been shown that the ovalbumin-induced responses are dependent upon the presence of mast cells. In the mast cell deficient mice, ovalbumin sensitization and challenge did not result in airway hyperresponsiveness and eosinophil influx. Second, the mast cell stabilizer, Cromolyn, was able to block the ovalbumin-induced airway hyperresponsiveness and inflammation (data not shown). The use of this model to evaluate
30 compounds for the treatment of asthmatic responses that may be mediated by mechanisms other than mast cell stabilization, is further supported by the inhibitory effect of the steroids, dexamethasone and budesonide, on methacholine-induced bronchoconstriction.

7.15.2 Results

The efficacy of R921304 was evaluated by intranasal administration on 10 consecutive days, from Day 7 through Day 16, at a dose level of 20 mg/kg, with the last 3 doses administered 30 minutes prior to either saline or ovalbumin challenge. R921304 was
5 able to inhibit the ovalbumin-induced airway hyperresponsiveness to methacholine when compared to the vehicle treated mice.

In a less stringent protocol, in which the mice were challenged with ovalbumin only once on Day 14, R921219 administered subcutaneously at 70 mg/kg in 67%PEG400/33% citrate buffer 30 minutes prior to saline or ovalbumin challenge, demonstrates that R921219
10 completely blocked the ovalbumin-induced airway hyperresponsiveness and cellular influx.

These results clearly demonstrate that R921219 and R921304 are efficacious in inhibiting the airway responses in a mouse model of allergic asthma.

7.16 2,4-Pyrimidinediamine Compounds Inhibit Phosphorylation of Proteins Downstream of Syk kinase in Activated Mast Cells

The inhibitory effect of the 2,4-pyrimidinediamine compounds on the phosphorylation of proteins downstream of Syk kinase was tested with compounds R921218, R218219 and R921304 in IgE receptor-activated BMMC cells.
15

For the assay, BMMC cells were incubated in the presence of varying concentrations of test compound (0.08 μ M, 0.4 μ M, 2 μ M and 10 μ M) for 1 hr at 37°C. The cells were
20 then stimulated with anti-IgE antibody as previously described. After 10 min, the cells were lysed and the cellular proteins separated by electrophoresis (SDS PAGE).

Following electrophoresis, the phosphorylation of the proteins indicated in FIGS. 7, 10 and 11A-D were assessed by immunoblot. Antibodies were purchased from Cell
25 Signaling Technology, Beverly, MA.

Referring to FIGS. 7, 10 and 11A-D, the indicated compounds tested inhibited phosphorylation of proteins downstream of Syk, but not upstream of Syk, in the IgE receptor signaling cascade, confirming both that the compounds inhibit upstream IgE induced degranulation, and that the compounds exert their inhibitory activity by inhibiting
30 Syk kinase.

7.17 2,4-Pyrimidinediamine Compounds Inhibit Syk Kinase in Biochemical Assays

Several 2,4-pyrimidinediamine compounds were tested for the ability to inhibit Syk kinase catalyzed phosphorylation of a peptide substrate in a biochemical fluorescenced polarization assay with isolated Syk kinase. In this experiment, Compounds were diluted to 1% DMSO in kinase buffer (20 mM HEPES, pH 7.4, 5 mM MgCl₂, 2 mM MnCl₂, 1 mM DTT, 0.1 mg/mL acetylated Bovine Gamma Globulin). Compound in 1% DMSO (0.2% DMSO final) was mixed with ATP/substrate solution at room temperature. Syk kinase (Upstate, Lake Placid NY) was added to a final reaction volume of 20 uL, and the reaction was incubated for 30 minutes at room temperature. Final enzyme reaction conditions were 20 mM HEPES, pH 7.4, 5 mM MgCl₂, 2 mM MnCl₂, 1 mM DTT, 0.1 mg/mL acetylated Bovine Gamma Globulin, 0.125 ng Syk, 4 uM ATP, 2.5 uM peptide substrate (biotin-EQEDEPEGDYEEVLE-CONH₂, SynPep Corporation). EDTA (10 mM final)/anti-phosphotyrosine antibody (1X final)/fluorescent phosphopeptide tracer (0.5X final) was added in FP Dilution Buffer to stop the reaction for a total volume of 40 uL according to manufacturer's instructions (PanVera Corporation) The plate was incubated for 30 minutes in the dark at room temperature. Plates were read on a Polarion fluorescence polarization plate reader (Tecan). Data were converted to amount of phosphopeptide present using a calibration curve generated by competition with the phosphopeptide competitor provided in the Tyrosine Kinase Assay Kit, Green (PanVera Corporation).

The results of the assay are shown in TABLE 6, below:

| TABLE 6 | |
|--------------|-------------------------------|
| Compound No. | IC ₅₀ (in μ M) |
| R926505 | 0.0703 |
| R926508 | 0.1315 |
| R926594 | 0.7705 |
| R926715 | 0.534 |
| R926745 | 0.0925 |
| R926782 | 0.1165 |
| R926791 | 0.207 |
| R926813 | 0.4047 |
| R926816 | 0.0615 |
| R935138 | 0.2288 |
| R935190 | 0.0465 |

| TABLE 6 | |
|--------------|-------------------|
| Compound No. | IC50 (in μ M) |
| R935191 | 0.045 |
| R935193 | 0.075 |
| R935194 | 0.1687 |
| R935196 | 0.2655 |
| R940255 | 0.7705 |
| R940256 | 2.787 |
| R940269 | 0.685 |
| R940275 | 0.7335 |
| R940276 | 0.1265 |
| R940277 | 0.2143 |
| R940290 | 0.187 |
| R945071 | 0.4295 |
| R945140 | 0.611 |
| R945142 | 2.007 |
| R945144 | 0.383 |
| R921302 | 0.2678 |
| R908702 | 0.0378 |
| R908712 | 0.024 |
| R909268 | 0.1253 |
| R920410 | 0.157 |
| R926753 | 0.108 |
| R926757 | 0.5103 |
| R926834 | 0.292 |
| R926839 | 0.055 |
| R926891 | 0.1695 |
| R926931 | 0.2553 |
| R935237 | 0.0455 |
| R935293 | 0.0465 |
| R935302 | 0.0265 |
| R935304 | 0.042 |
| R935307 | 0.057 |
| R935309 | 0.098 |
| R935310 | 0.2003 |
| R940323 | 0.062 |
| R940338 | 0.028 |

| TABLE 6 | |
|--------------|-------------------------------|
| Compound No. | IC ₅₀ (in μ M) |
| R921303 | 0.00045 |
| R940347 | 0.0345 |
| R921304 | 0.01275 |
| R950368 | 0.0107 |
| R950373 | 0.0665 |

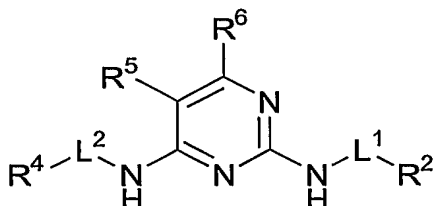
These data demonstrate that all of the compounds tested, except for R945142 and R909236 inhibit Syk kinase phosphorylation with IC₅₀s in the submicromolar range. All compounds tested inhibit Syk kinase phosphorylation with IC₅₀s in the micromolar range.

5 Although the foregoing invention has been described in some detail to facilitate understanding, it will be apparent that certain changes and modifications may be practiced within the scope of the appended claims. Accordingly, the described embodiments are to be considered as illustrative and not restrictive, and the invention is not to be limited to the details given herein, but may be modified within the scope and equivalents of the appended
10 claims.

 All literature and patent references cited throughout the application are incorporated by reference into the application for all purposes.

What is Claimed Is:

1. A compound according to structural formula (I):



and salts, hydrates, solvates, N-oxides and prodrugs thereof, wherein:

L^1 and L^2 are each, independently of one another, selected from the group consisting of a direct bond and a linker;

R^2 is selected from the group consisting of (C1-C6) alkyl optionally substituted with one or more of the same or different R^8 groups, (C3-C8) cycloalkyl optionally substituted with one or more of the same or different R^8 groups, cyclohexyl optionally substituted with one or more of the same or different R^8 groups, 3-8 membered cycloheteroalkyl optionally substituted with one or more of the same or different R^8 groups, (C5-C15) aryl optionally substituted with one or more of the same or different R^8 groups, phenyl optionally substituted with one or more of the same or different R^8 groups and 5-15 membered heteroaryl optionally substituted with one or more of the same or different R^8 groups;

R^4 is selected from the group consisting of hydrogen, (C1-C6) alkyl optionally substituted with one or more of the same or different R^8 groups, (C3-C8) cycloalkyl optionally substituted with one or more of the same or different R^8 groups, cyclohexyl optionally substituted with one or more of the same or different R^8 groups, 3-8 membered cycloheteroalkyl optionally substituted with one or more of the same or different R^8 groups, (C5-C15) aryl optionally substituted with one or more of the same or different R^8 groups, phenyl optionally substituted with one or more of the same or different R^8 groups and 5-15 membered heteroaryl optionally substituted with one or more of the same or different R^8 groups;

R^5 is selected from the group consisting of R^6 , (C1-C6) alkyl optionally substituted with one or more of the same or different R^8 groups, (C1-C4) alkanyl optionally substituted with one

or more of the same or different R^8 groups, (C2-C4) alkenyl optionally substituted with one or more of the same or different R^8 groups and (C2-C4) alkynyl optionally substituted with one or more of the same or different R^8 groups;

each R^6 is independently selected from the group consisting of hydrogen, an electronegative group, $-OR^d$, $-SR^d$, (C1-C3) haloalkyloxy, (C1-C3) perhaloalkyloxy, $-NR^cR^c$, halogen, (C1-C3) haloalkyl, (C1-C3) perhaloalkyl, $-CF_3$, $-CH_2CF_3$, $-CF_2CF_3$, $-CN$, $-NC$, $-OCN$, $-SCN$, $-NO$, $-NO_2$, $-N_3$, $-S(O)R^d$, $-S(O)_2R^d$, $-S(O)_2OR^d$, $-S(O)NR^cR^c$, $-S(O)_2NR^cR^c$, $-OS(O)R^d$, $-OS(O)_2R^d$, $-OS(O)_2OR^d$, $-OS(O)NR^cR^c$, $-OS(O)_2NR^cR^c$, $-C(O)R^d$, $-C(O)OR^d$, $-C(O)NR^cR^c$, $-C(NH)NR^cR^c$, $-OC(O)R^d$, $-SC(O)R^d$, $-OC(O)OR^d$, $-SC(O)OR^d$, $-OC(O)NR^cR^c$, $-SC(O)NR^cR^c$, $-OC(NH)NR^cR^c$, $-SC(NH)NR^cR^c$, $-[NHC(O)]_nR^d$, $-[NHC(O)]_nOR^d$, $-[NHC(O)]_nNR^cR^c$ and $-[NHC(NH)]_nNR^cR^c$, (C5-C10) aryl optionally substituted with one or more of the same or different R^8 groups, phenyl optionally substituted with one or more of the same or different R^8 groups, (C6-C16) arylalkyl optionally substituted with one or more of the same or different R^8 groups, 5-10 membered heteroaryl optionally substituted with one or more of the same or different R^8 groups and 6-16 membered heteroarylalkyl optionally substituted with one or more of the same or different R^8 groups;

R^8 is selected from the group consisting of R^a , R^b , R^a substituted with one or more of the same or different R^a or R^b , $-OR^a$ substituted with one or more of the same or different R^a or R^b , $-B(OR^a)_2$, $-B(NR^cR^c)_2$, $-(CH_2)_mR^b$, $-(CHR^a)_mR^b$, $-O-(CH_2)_mR^b$, $-S-(CH_2)_mR^b$, $-O-CHR^aR^b$, $-O-CR^a(R^b)_2$, $-O-(CHR^a)_mR^b$, $-O-(CH_2)_m-CH[(CH_2)_mR^b]R^b$, $-S-(CHR^a)_mR^b$, $-C(O)NH-(CH_2)_mR^b$, $-C(O)NH-(CHR^a)_mR^b$, $-O-(CH_2)_m-C(O)NH-(CH_2)_mR^b$, $-S-(CH_2)_m-C(O)NH-(CH_2)_mR^b$, $-O-(CHR^a)_m-C(O)NH-(CHR^a)_mR^b$, $-S-(CHR^a)_m-C(O)NH-(CHR^a)_mR^b$, $-NH-(CH_2)_mR^b$, $-NH-(CHR^a)_mR^b$, $-NH[(CH_2)_mR^b]$, $-N[(CH_2)_mR^b]_2$, $-NH-C(O)-NH-(CH_2)_mR^b$, $-NH-C(O)-(CH_2)_m-CHR^bR^b$ and $-NH-(CH_2)_m-C(O)-NH-(CH_2)_mR^b$;

each R^a is independently selected from the group consisting of hydrogen, (C1-C6) alkyl, (C3-C8) cycloalkyl, cyclohexyl, (C4-C11) cycloalkylalkyl, (C5-C10) aryl, phenyl, (C6-C16) arylalkyl, benzyl, 2-6 membered heteroalkyl, 3-8 membered cycloheteroalkyl, morpholinyl, piperazinyl, homopiperazinyl, piperidinyl, 4-11 membered cycloheteroalkylalkyl, 5-10 membered heteroaryl and 6-16 membered heteroarylalkyl;

each R^b is a suitable group independently selected from the group consisting of $=O$, $-OR^d$, (C1-C3) haloalkyloxy, $-OCF_3$, $=S$, $-SR^d$, $=NR^d$, $=NOR^d$, $-NR^cR^c$, halogen, $-CF_3$, $-CN$, $-NC$, $-OCN$, $-SCN$, $-NO$, $-NO_2$, $=N_2$, $-N_3$, $-S(O)R^d$, $-S(O)_2R^d$, $-S(O)_2OR^d$, $-S(O)NR^cR^c$, $-S(O)_2NR^cR^c$, $-OS(O)R^d$, $-OS(O)_2R^d$, $-OS(O)_2OR^d$, $-OS(O)_2NR^cR^c$, $-C(O)R^d$, $-C(O)OR^d$, $-C(O)NR^cR^c$, $-C(NH)NR^cR^c$, $-C(NR^a)NR^cR^c$, $-C(NOH)R^a$, $-C(NOH)NR^cR^c$, $-OC(O)R^d$, $-OC(O)OR^d$, $-OC(O)NR^cR^c$, $-OC(NH)NR^cR^c$, $-OC(NR^a)NR^cR^c$, $-[NHC(O)]_nR^d$, $-[NR^aC(O)]_nR^d$, $-[NHC(O)]_nOR^d$, $-[NR^aC(O)]_nOR^d$, $-[NHC(O)]_nNR^cR^c$, $-[NR^aC(O)]_nNR^cR^c$, $-[NHC(NH)]_nNR^cR^c$ and $-[NR^aC(NR^a)]_nNR^cR^c$;

each R^c is independently a protecting group or R^a , or, alternatively, each R^c is taken together with the nitrogen atom to which it is bonded to form a 5 to 8-membered cycloheteroalkyl or heteroaryl which may optionally include one or more of the same or different additional heteroatoms and which may optionally be substituted with one or more of the same or different R^a or suitable R^b groups;

each R^d is independently a protecting group or R^a ;

each m is independently an integer from 1 to 3; and

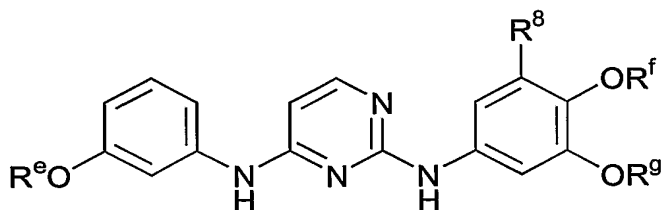
each n is independently an integer from 0 to 3,

with the provisos that:

- (1) when L^1 is a direct bond and R^6 is hydrogen, then R^2 is not 3,4,5-tri (C1-C6) alkoxyphenyl;
- (2) when L^1 and L^2 are each a direct bond, R^2 is a substituted phenyl and R^6 is hydrogen, then R^5 is other than cyano or $-C(O)NHR$, where R is hydrogen or (C1-C6) alkyl;
- (3) when L^1 and L^2 are each a direct bond and R^2 and R^4 are each independently a substituted or unsubstituted pyrrole or indole, then the R^2 and R^4 are attached to the remainder of the molecule *via* a ring carbon atom; and
- (4) the compound is not
 - N2,N4-bis(4-ethoxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R070790);
 - N2,N4-bis(2-methoxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R081166);
 - N2,N4-bis(4-methoxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R088814);
 - N2,N4-bis(2-chlorophenyl)-5-fluoro-2,4-pyrimidinediamine (R088815);
 - N2,N4-bisphenyl-5-fluoro-2,4-pyrimidinediamine (R091880);

N2,N4-bis(3-methylphenyl)-5-fluoro-2,4-pyrimidinediamine (R092788);
N2,N4-bis(3-chlorophenyl)-5-fluoro-2,4-pyrimidinediamine (R067962);
N2,N4-bis(2,5-dimethylphenyl)-5-fluoro-2,4-pyrimidinediamine (R067963);
N2,N4-bis(3,4-dimethylphenyl)-5-fluoro-2,4-pyrimidinediamine (R067964);
N2,N4-bis(4-chlorophenyl)-5-fluoro-2,4-pyrimidinediamine (R070153);
N2,N4-bis(2,4-dimethylphenyl)-5-fluoro-2,4-pyrimidinediamine (R070791);
N2,N4-bis(3-bromophenyl)-5-fluoro-2,4-pyrimidinediamine (R008958);
N2,N4-bis(phenyl)-5-fluoro-2,4-pyrimidinediamine;
N2,N4-bis(morpholino)-5-fluoro-2,4-pyrimidinediamine;
N2,N4-bis[(3-chloro-4-methoxyphenyl)]-5-fluoro-2,4-pyrimidinediamine; N2-(3,4,5-trimethoxyphenyl)-N4-(3,5-dimethoxyphenyl)-2,4-pyrimidinediamine; N2-(3,4-dimethoxyphenyl)-N4-(3-methoxyphenyl)-2,4-pyrimidinediamine; N2,N4-bis(3,4-dimethoxyphenyl)-2,4-pyrimidinediamine; N2,N4-Bis(3-chloro-4-methoxy-5-fluoro-2,4-pyrimidinediamine; N2-[4-(3-dimethylamino-2-hydroxy-propyloxy)phenyl]-N4-3,4-dichlorophenyl-5-chloro-2,4-pyrimidinediamine; N2-[4-(3-dimethylamino-2-hydroxy-propyloxy)phenyl]-N4-3,4-dichlorophenyl-2,4-pyrimidinediamine; N2-[4-(3-dimethylamino-2-hydroxy-propyloxy)phenyl]-N4-3,4-dichlorophenyl-5-methyl-2,4-pyrimidinediamine; N2-(4-benzoxoxyphenyl)-N4-(3,4,5-trimethoxyphenyl)-2,4-pyrimidinediamine; N2,N4-bis(3,4,5-trimethoxyphenyl)-2,4-pyrimidinediamine; N2,N4-bis(3,4,5-trimethoxyphenyl)-5-bromo-2,4-pyrimidinediamine; N2-(1-benzyl-1H-indazol-5-yl)-N4-(3,4,5-trimethoxyphenyl)-2,4-pyrimidinediamine; N2-(1H-indol-1-yl)-N4-(3,4,5-trimethoxyphenyl)-2,4-pyrimidinediamine; N2-[(2-methoxy-5-aminosulfonyl)phenyl]-N4-(3-methyl-1H-indazol-6-yl)-2,4-pyrimidinediamine; N2-[2-methoxy-5-(5-methyl-3-isoxazolyl-methylsulfonyl)phenyl]-N4-(3-methyl-1H-indazol-6-yl)-2,4-pyrimidinediamine; N2-[(2-methoxy-5-methylaminosulfonyl)phenyl]-N4-(3-methyl-1H-indazol-6-yl)-2,4-pyrimidinediamine; N2-[(2-methoxy-5-ethylsulfonyl)phenyl]-N4-(3-methyl-1H-indazol-6-yl)-2,4-pyrimidinediamine; N2-[(2-methoxy-5-isobutylsulfonyl)phenyl]-N4-(3-methyl-1H-indazol-6-yl)-2,4-pyrimidinediamine; N2-[(2-methoxy-5-propylcarbonyl)phenyl]-N4-(3-methyl-1H-indazol-6-yl)-2,4-pyrimidinediamine; N2-(1H-indazol-5-yl)-N4-propynyl-5-bromo-2,4-pyrimidinediamine; N2-(1-H-indol-5-yl)-N4-[1-(3-methyl-1-hydroxy)butyl]-N4-(1H-indol-5-yl)-5-bromo-2,4-pyrimidinediamine; N2-(1-dimethylaminosulfonyl-1H-indol-5-yl)-N4-[1-(2-

methyl-2-hydroxy)ethyl]-5-bromo-2,4-pyrimidinediamine, or a compound according to the formula:



wherein: R^e is (C1-C6) alkyl; R^f and R^g are each, independently of one another, a straight-chain or branched (C1-C6) alkyl which is optionally substituted with one or more of the same or different R^8 groups; and R^8 is as defined above.

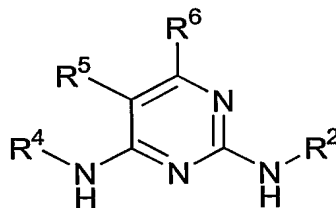
2. The compound of Claim 1 in which L^1 and L^2 are each, independently of one another, selected from the group consisting of a direct bond, (C1-C3) alkylidyl optionally substituted with one or more of the same or different R^9 groups and 1-3 membered heteroalkylidyl optionally substituted with one or more of the same or different R^9 groups, wherein:

R^9 is selected from the group consisting of (C1-C3) alkyl, $-OR^a$, $-C(O)OR^a$, (C5-C10) aryl optionally substituted with one or more of the same or different halogens, phenyl optionally substituted with one or more of the same or different halogens, 5-10 membered heteroaryl optionally substituted with one or more of the same or different halogens and 6 membered heteroaryl optionally substituted with one or more of the same or different halogens; and

R^a is as defined in Claim 1.

3. The compound of Claim 2 in which L^1 and L^2 are each, independently of one another, selected from the group consisting of methano, ethano and propano, each of which may be optionally monosubstituted with an R^9 group.

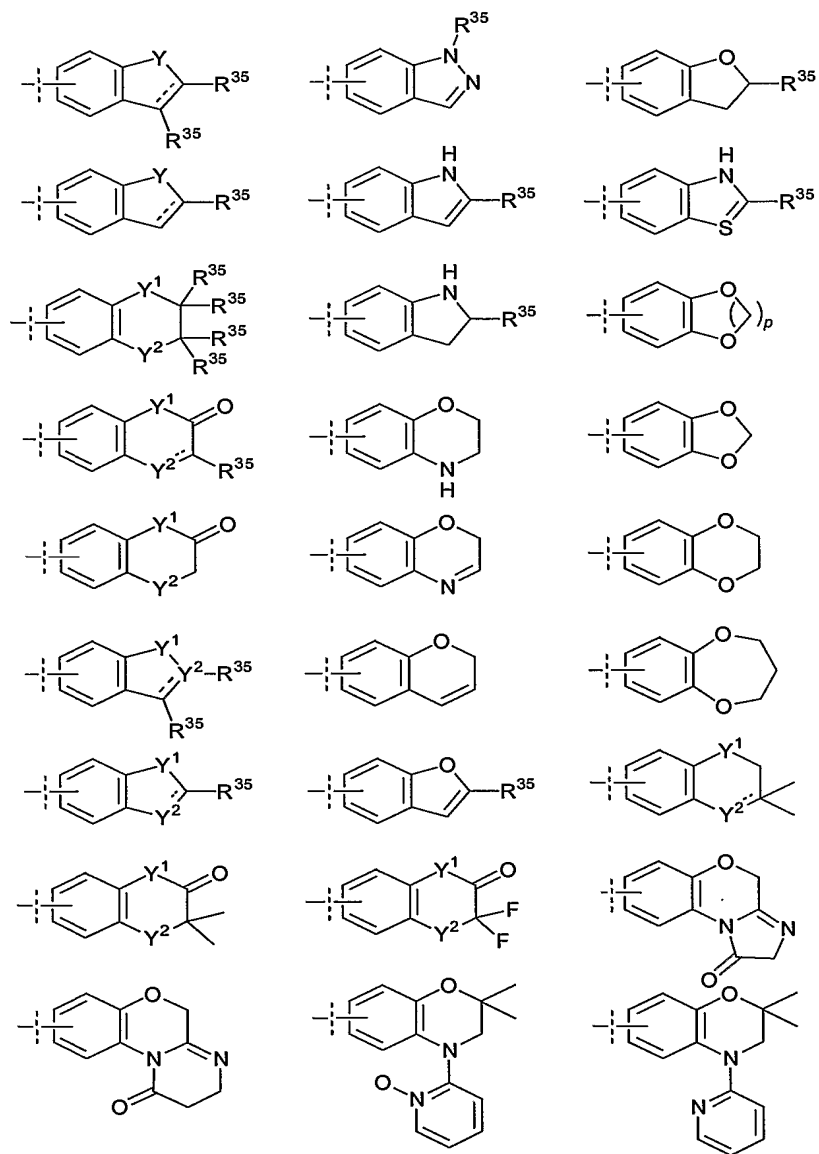
4. The compound of Claim 3 in which the R^9 group is selected from the group consisting of $-OR^a$, $-C(O)OR^a$, halophenyl and 4-halophenyl, wherein R^a is as defined in Claim 1.
5. The compound of Claim 1 in which R^6 is hydrogen.
6. The compound of Claim 1 or 5 in which R^5 is selected from the group consisting of an electronegative group, halo, $-F$, $-CN$, $-NO_2$, $-C(O)R^a$, $-C(O)OR^a$, $-C(O)CF_3$, $-C(O)OCF_3$, (C1-C3) haloalkyl, (C1-C3) perhaloalkyl (C1-C3) haloalkoxy, (C1-C3) perhaloalkoxy, $-OCF_3$ and $-CF_3$.
7. The compound of Claim 1 in which at least one of L1 or L2 is a direct bond.
8. The compound of Claim 1 according to the structure (Ia):

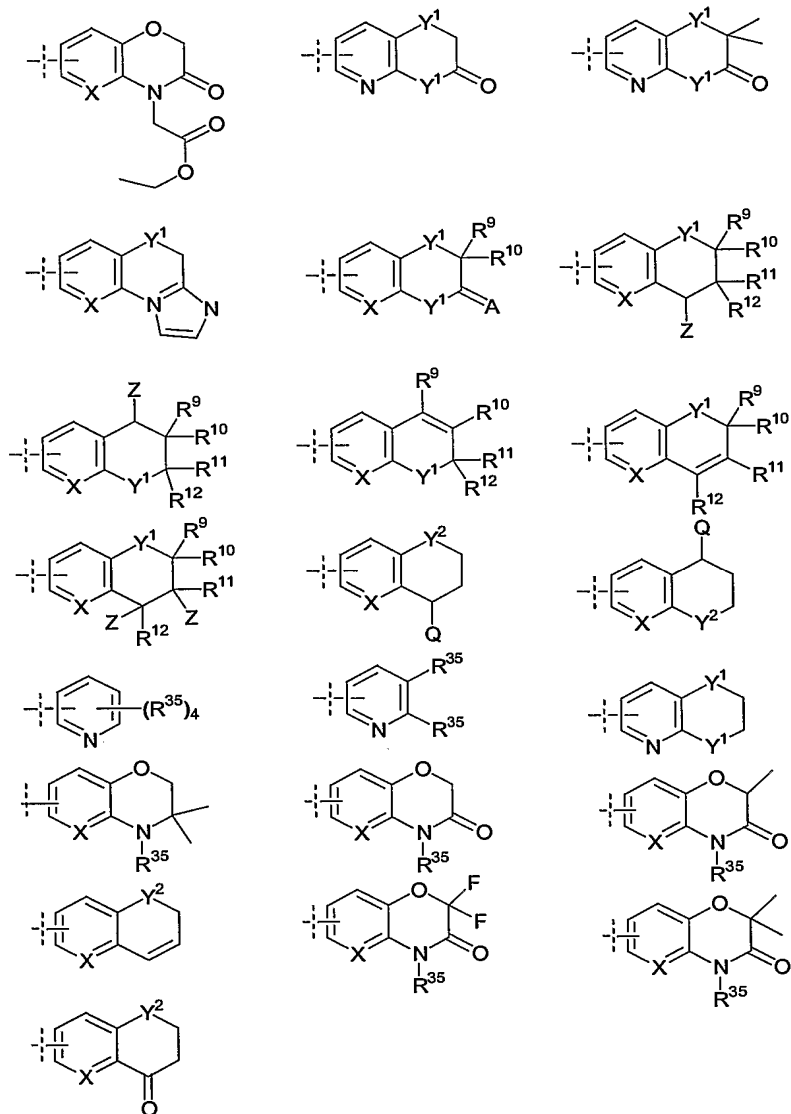


and salts, hydrates, solvates, N-oxides and prodrugs thereof, wherein R^2 , R^4 , R^5 and R^6 are as defined in Claim 1.

9. The compound of Claim 8 in which R^2 is selected from the group consisting of phenyl, naphthyl, 5-10 membered heteroaryl, benzodioxanyl, 1,4-benzodioxan-(5 or 6)-yl, benzodioxolyl, 1,3-benzodioxol-(4 or 5)-yl, benzoxazinyl, 1,4-benzoxazin-(5,6,7 or 8)-yl, benzoxazolyl, 1,3-benzoxazol-(4,5,6 or 7)-yl, benzopyranyl, benzopyran-(5,6,7 or 8)-yl, benzotriazolyl, benzotriazol-(4,5,6 or 7)-yl, 1,4-benzoxazinyl-2-one, 1,4-benzoxazin-(5,6,7 or 8)-yl-2-one, 2H-1,4-benzoxazinyl-3(4H)-one, 2H-1,4-benzoxazin-(5,6,7 or 8)-yl-3(4H)-one, 2H-1,3-benzoxazinyl-2,4(3H)-dione, 2H-1,3-benzoxazin-(5,6,7 or 8)-yl-2,4(3H)-dione, benzoxazolyl-2-one, benzoxazol-(4,5,6 or 7)-yl-2-one, dihydrocoumarinyl, dihydrocoumarin-(5,6,7 or 8)-yl, 1,2-benzopyronyl, 1,2-benzopyron-(5,6,7 or 8)-yl, benzofuranyl, benzofuran-(4,5,6 or 7)-yl, benzo[b]furanyl, benzo[b]furan-(4,5,6 or 7)-yl, indolyl, indol-(4,5,6 or 7)-yl, pyrrolyl and pyrrol-(1 or 2)-yl, each of which may be optionally substituted with one or more of the same or different R^8 groups, where R^8 is as defined in Claim 1.

10. The compound of Claim 8 in which R^2 and/or R^4 are each, independently of one another, a heteroaryl selected from the group consisting of:





wherein:

p is an integer from one to three;

each --- independently represents a single bond or a double bond;

R^{35} is hydrogen or R^8 , where R^8 is as previously defined for structural formula

(I);

X is selected from the group consisting of CH, N and N-O;

each Y is independently selected from the group consisting of O, S and NH;

each Y^1 is independently selected from the group consisting of O, S, SO, SO₂, SONR³⁶, NH and NR³⁷;

each Y^2 is independently selected from the group consisting of CH, CH₂, O, S, N, NH and NR³⁷;

R³⁶ is hydrogen or alkyl;

R³⁷ is selected from the group consisting of hydrogen and a progroup, preferably hydrogen or a progroup selected from the group consisting of aryl, arylalkyl, heteroaryl, R^a, R^b-CR^aR^b-O-C(O)R⁸, -CR^aR^b-O-PO(OR⁸)₂, -CH₂-O-PO(OR⁸)₂, -CH₂-PO(OR⁸)₂, -C(O)-CR^aR^b-N(CH₃)₂, -CR^aR^b-O-C(O)-CR^aR^b-N(CH₃)₂, -C(O)R⁸, -C(O)CF₃ and -C(O)-NR⁸-C(O)R⁸;

R³⁸ is selected from the group consisting of alkyl and aryl;

A is selected from the group consisting of O, NH and NR³⁸;

R⁹, R¹⁰, R¹¹ and R¹² are each, independently of one another, selected from the group consisting of alkyl, alkoxy, halogen, haloalkoxy, aminoalkyl and hydroxyalkyl, or, alternatively, R⁹ and R¹⁰ and/or R¹¹ and R¹² are taken together form a ketal;

each Z is selected from the group consisting of hydroxyl, alkoxy, aryloxy, ester, carbamate and sulfonyl;

Q is selected from the group consisting of -OH, OR⁸, -NR^cR^c, -NHR³⁹-C(O)R⁸, -NHR³⁹-C(O)OR⁸, -NR³⁹-CHR⁴⁰-R^b, -NR³⁹-(CH₂)_m-R^b and -NR³⁹-C(O)-CHR⁴⁰-NR^cR^c;

R³⁹ and R⁴⁰ are each, independently of one another, selected from the group consisting of hydrogen, alkyl, aryl, alkylaryl; arylalkyl and NHR⁸; and

R^a, R^b and R^c are as previously defined for structural formula (I).

11. The compound of Claim 10 in which R² and R⁴ are the same.

12. The compound of Claim 10 or 11 in which each R³⁵ is independently selected from the group consisting of hydrogen, R^d, -NR^cR^c, -(CH₂)_m-NR^cR^c, -C(O)NR^cR^c, -(CH₂)_m-C(O)NR^cR^c, -C(O)OR^d, -(CH₂)_m-C(O)OR^d and -(CH₂)_m-OR^d, where *m*, R^c and R^d are as defined in Claim 1.

13. The compound of Claim 12 in which each *m* is one.

14. The compound of Claim 8 in which R^2 is an optionally substituted heteroaryl which is attached to the remainder of the molecule *via* a ring carbon atom.

15. The compound of Claim 8 in which R^4 is an optionally substituted heteroaryl which is attached to the remainder of the molecule *via* a ring carbon atom.

16. The compound of Claim 8 in which R^2 and/or R^4 are each, independently of one another, a phenyl optionally substituted with one, two or three R^8 groups, where R^8 is as defined in Claim 1.

17. The compound of Claim 16 in which R^2 and R^4 are each the same or different optionally substituted phenyl.

18. The compound of Claim 16 or 17 in which the optionally substituted phenyl is *mono* substituted.

19. The compound of Claim 18 in which the R^8 substituent is at the *ortho*, *meta* or *para* position.

20. The compound of Claim 19 in which R^8 is selected from the group consisting of (C1-C10) alkyl, (C1-C10) branched alkyl, $-OR^d$, $-O-(CH_2)_m-NR^cR^c$, $-O-C(O)NR^cR^c$, $-O-(CH_2)_m-C(O)NR^cR^c$, $-O-C(O)OR^a$, $-O-(CH_2)_m-C(O)OR^a$, $-O-C(NH)NR^cR^c$, $-O-(CH_2)_m-C(NH)NR^cR^c$, $-NH-(CH_2)_m-NR^cR^c$, $-NH-C(O)NR^cR^c$ and $-NH-(CH_2)_m-C(O)NR^cR^c$, where m , R^a , R^c and R^d are as defined in Claim 1.

21. The compound of Claim 16 or 17 in which the optionally substituted phenyl is a disubstituted phenyl.

22. The compound of Claim 21 in which the R^8 substituents are positioned 2,3-; 2,4-; 2,5-; 2,6-; 3,4-; or 3,5-.

23. The compound of Claim 21 in which each R^8 is independently selected from the group consisting of (C1-C10) alkyl, (C1-C10) branched alkyl, $-OR^a$ optionally substituted with

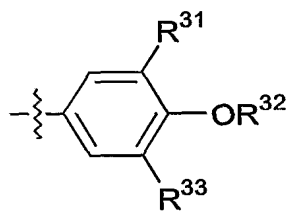
one or more of the same or different R^a or R^b groups, $-O-(CH_2)_m-NR^cR^c$, $-O-C(O)NR^cR^c$, $-O-(CH_2)_m-C(O)NR^cR^c$, $-O-C(O)OR^a$, $-O-(CH_2)_m-C(O)OR^a$, $-O-C(NH)NR^cR^c$, $-O-(CH_2)_m-C(NH)NR^cR^c$, $-NH-(CH_2)_m-NR^cR^c$, $-NH-C(O)NR^cR^c$ and $-NH-(CH_2)_m-C(O)NR^cR^c$, where m , R^a , R^b and R^c are as defined in Claim 1.

24. The compound of Claim 16 or 17 in which the optionally substituted phenyl is trisubstituted.

25. The compound of Claim 24 in which the R^8 substituents are positioned 2,3,4; 2,3,5; 2,3,6; 2,4,5; 2,4,6; 2,5,6; or 3,4,5.

26. The compound of Claim 25 which each R^8 is independently selected from the group consisting of (C1-C10) alkyl, (C1-C10) branched alkyl, $-OR^a$ optionally substituted with one or more of the same or different R^a or R^b groups, $-O-(CH_2)_m-NR^cR^c$, $-O-C(O)NR^cR^c$, $-O-(CH_2)_m-C(O)NR^cR^c$, $-O-C(O)OR^a$, $-O-C(NH)NR^cR^c$, $-O-(CH_2)_m-C(O)OR^a$, $-O-(CH_2)_m-C(NH)NR^cR^c$, $-NH-(CH_2)_m-NR^cR^c$, $-NH-C(O)NR^cR^c$ and $-NH-(CH_2)_m-C(O)NR^cR^c$, where m , R^a , R^b and R^c are as defined in Claim 1.

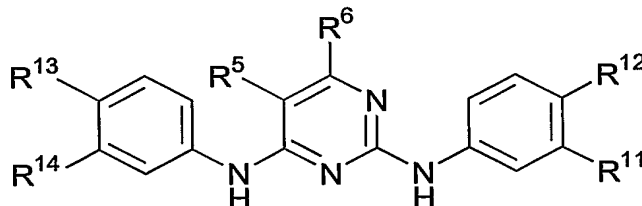
27. The compound of Claim 24 in which the trisubstituted phenyl has the formula:



wherein: R^{31} is methyl or (C1-C6) alkyl; R^{32} is hydrogen, methyl or (C1-C6) alkyl; and R^{33} is a halo group.

28. The compound of Claim 17 in which R^2 and R^4 are the same.

29. The compound of Claim 8 according to structural formula (Ib):

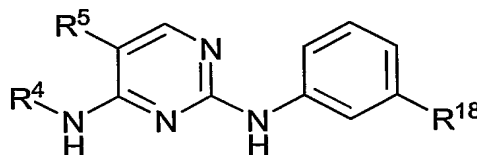


and salts, hydrates, solvates and N-oxides thereof, wherein R^{11} , R^{12} , R^{13} and R^{14} are each, independently of one another, selected from the group consisting of hydrogen, hydroxy, (C1-C6) alkoxy and $-NR^cR^c$; and R^5 , R^6 and R^c are as defined in Claim 1.

30. The compound of Claim 29 in which R^{11} , R^{12} , R^{13} and R^{14} are each hydrogen.

31. The compound of Claim 29 in which R^{12} and R^{13} are each hydrogen.

32. The compound of Claim 8 according to structural formula (Ic):



and salts, hydrates, solvates, N-oxides and prodrugs thereof, wherein:

R^4 is phenyl optionally substituted with from 1 to 3 of the same or different R^8 groups or 5-14 membered heteroaryl optionally substituted with from 1 to 4 of the same or different R^8 groups;

R^5 is an electronegative group, F or CF_3 ; and

R^{18} is $-O(CH_2)_m-R^b$, where m and R^b are as defined in Claim 1.

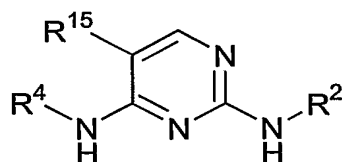
33. The compound of Claim 32 in which R^4 is an optionally substituted heteroaryl.

34. The compound of Claim 32 in which R¹⁸ is -O-CH₂-C(O)-NHCH₃.

35. The compound of Claim 1 which inhibits mast cell or basophil cell degranulation as measured in an *in vitro* assay.

36. The compound of Claim 35 which has an IC₅₀ of about 20 μM or less.

37. A compound according to structural formula (Id):



and salts, hydrates, solvates, N-oxides and prodrugs thereof, wherein:

R² and R⁴ are as defined in Claim 1; and

R¹⁵ is an electronegative group,

with the provisos that:

(1) when R² is 3,4,5-tri (C1-C6) alkoxyphenyl and R¹⁵ is halogen, then R⁴ is not 3,4,5-tri (C1-C6) alkoxyphenyl;

(2) when R² is a substituted phenyl group, then R¹⁵ is other than cyano or -C(O)NHR, where R is hydrogen or (C1-C6) alkyl; and

(3) the compound is not

N2,N4-bis(4-ethoxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R070790);

N2,N4-bis(2-methoxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R081166);

N2,N4-bis(4-methoxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R088814);

N2,N4-bis(2-chlorophenyl)-5-fluoro-2,4-pyrimidinediamine (R088815);

N2,N4-bisphenyl-5-fluoro-2,4-pyrimidinediamine (R091880);

N2,N4-bis(3-methylphenyl)-5-fluoro-2,4-pyrimidinediamine (R092788);

N2,N4-bis(3-chlorophenyl)-5-fluoro-2,4-pyrimidinediamine (R067962);

N2,N4-bis(2,5-dimethylphenyl)-5-fluoro-2,4-pyrimidinediamine (R067963);

N2,N4-bis(3,4-dimethylphenyl)-5-fluoro-2,4-pyrimidinediamine (R067964);

N2,N4-bis(4-chlorophenyl)-5-fluoro-2,4-pyrimidinediamine (R0707153);
N2,N4-bis(2,4-dimethylphenyl)-5-fluoro-2,4-pyrimidinediamine (R070791);
N2,N4-bis(3-bromophenyl)-5-fluoro-2,4-pyrimidinediamine (R008958);
N2,N4-bis(phenyl)-5-fluoro-2,4-pyrimidinediamine;
N2,N4-bis(morpholino)-5-fluoro-2,4-pyrimidinediamine; or
N2,N4-bis[(3-chloro-4-methoxyphenyl)]-5-fluoro-2,4-pyrimidinediamine.

38. The compound of Claim 37 in which when R¹⁵ is halogen or nitro, then R² is not 3,4,5-tri (C1-C6) alkoxyphenyl.

39. The compound of Claim 38 in which R¹⁵ is selected from the group consisting of –CN, –NC, –NO₂, halogen, –F, (C1-C3) haloalkyl, (C1-C3) perhaloalkyl, (C1-C3) fluoroalkyl, (C1-C3) perfluoroalkyl, –CF₃, (C1-C3) haloalkoxy, (C1-C3) perhaloalkoxy, (C1-C3) fluoroalkoxy, (C1-C3) perfluoroalkoxy and –OCF₃.

40. The compound of Claim 39 in which R¹⁵ is selected from the group consisting of halo, Br, F, –CF₃ and –NO₂.

41. The compound of Claim 37 which inhibits mast cell or basophil cell degranulation as measured in an *in vitro* assay.

42. The compound of Claim 41 which has an IC₅₀ of about 20 μM or less.

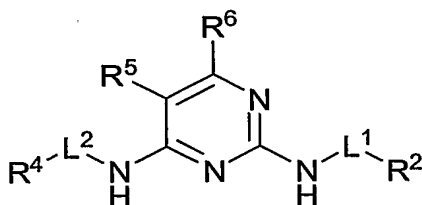
43. A compound selected from any compound in TABLE 1 which inhibits mast cell or basophil cell degranulation as measured in an *in vitro* assay, with the proviso that the compound is not

N2,N4-bis(4-ethoxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R070790);
N2,N4-bis(2-methoxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R081166);
N2,N4-bis(4-methoxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R088814);
N2,N4-bis(2-chlorophenyl)-5-fluoro-2,4-pyrimidinediamine (R088815);
N2,N4-bisphenyl-5-fluoro-2,4-pyrimidinediamine (R091880);

N2,N4-bis(3-methylphenyl)-5-fluoro-2,4-pyrimidinediamine (R092788);
 N2,N4-bis(3-chlorophenyl)-5-fluoro-2,4-pyrimidinediamine (R067962);
 N2,N4-bis(2,5-dimethylphenyl)-5-fluoro-2,4-pyrimidinediamine (R067963);
 N2,N4-bis(3,4-dimethylphenyl)-5-fluoro-2,4-pyrimidinediamine (R067964);
 N2,N4-bis(4-chlorophenyl)-5-fluoro-2,4-pyrimidinediamine (R070153);
 N2,N4-bis(2,4-dimethylphenyl)-5-fluoro-2,4-pyrimidinediamine (R070791); or
 N2,N4-bis(3-bromophenyl)-5-fluoro-2,4-pyrimidinediamine (R008958).

44. The compound of Claim 43 which has an IC_{50} of about 20 μM or less.

45. A pharmaceutical composition comprising a pyrimidinediamine compound and a pharmaceutically acceptable excipient, carrier or diluent, said pyrimidinediamine compound being a compound according to structural formula (I):



and salts, hydrates, solvates, N-oxides and prodrugs thereof, wherein:

L^1 and L^2 are each, independently of one another, selected from the group consisting of a direct bond and a linker;

R^2 is selected from the group consisting of (C1-C6) alkyl optionally substituted with one or more of the same or different R^8 groups, (C3-C8) cycloalkyl optionally substituted with one or more of the same or different R^8 groups, cyclohexyl optionally substituted with one or more of the same or different R^8 groups, 3-8 membered cycloheteroalkyl optionally substituted with one or more of the same or different R^8 groups, (C5-C15) aryl optionally substituted with one or more of the same or different R^8 groups, phenyl optionally substituted with one or more

of the same or different R^8 groups and 5-15 membered heteroaryl optionally substituted with one or more of the same or different R^8 groups;

R^4 is selected from the group consisting of hydrogen, (C1-C6) alkyl optionally substituted with one or more of the same or different R^8 groups, (C3-C8) cycloalkyl optionally substituted with one or more of the same or different R^8 groups, cyclohexyl optionally substituted with one or more of the same or different R^8 groups, 3-8 membered cycloheteroalkyl optionally substituted with one or more of the same or different R^8 groups, (C5-C15) aryl optionally substituted with one or more of the same or different R^8 groups, phenyl optionally substituted with one or more of the same or different R^8 groups and 5-15 membered heteroaryl optionally substituted with one or more of the same or different R^8 groups;

R^5 is selected from the group consisting of R^6 , (C1-C6) alkyl optionally substituted with one or more of the same or different R^8 groups, (C1-C4) alkanyl optionally substituted with one or more of the same or different R^8 groups, (C2-C4) alkenyl optionally substituted with one or more of the same or different R^8 groups and (C2-C4) alkynyl optionally substituted with one or more of the same or different R^8 groups;

each R^6 is independently selected from the group consisting of hydrogen, an electronegative group, $-OR^d$, $-SR^d$, (C1-C3) haloalkyloxy, (C1-C3) perhaloalkyloxy, $-NR^cR^c$, halogen, (C1-C3) haloalkyl, (C1-C3) perhaloalkyl, $-CF_3$, $-CH_2CF_3$, $-CF_2CF_3$, $-CN$, $-NC$, $-OCN$, $-SCN$, $-NO$, $-NO_2$, $-N_3$, $-S(O)R^d$, $-S(O)_2R^d$, $-S(O)_2OR^d$, $-S(O)NR^cR^c$, $-S(O)_2NR^cR^c$, $-OS(O)R^d$, $-OS(O)_2R^d$, $-OS(O)_2OR^d$, $-OS(O)NR^cR^c$, $-OS(O)_2NR^cR^c$, $-C(O)R^d$, $-C(O)OR^d$, $-C(O)NR^cR^c$, $-C(NH)NR^cR^c$, $-OC(O)R^d$, $-SC(O)R^d$, $-OC(O)OR^d$, $-SC(O)OR^d$, $-OC(O)NR^cR^c$, $-SC(O)NR^cR^c$, $-OC(NH)NR^cR^c$, $-SC(NH)NR^cR^c$, $-[NHC(O)]_nR^d$, $-[NHC(O)]_nOR^d$, $-[NHC(O)]_nNR^cR^c$ and $-[NHC(NH)]_nNR^cR^c$, (C5-C10) aryl optionally substituted with one or more of the same or different R^8 groups, phenyl optionally substituted with one or more of the same or different R^8 groups, (C6-C16) arylalkyl optionally substituted with one or more of the same or different R^8 groups, 5-10 membered heteroaryl optionally substituted with one or more of the same or different R^8 groups and 6-16 membered heteroarylalkyl optionally substituted with one or more of the same or different R^8 groups;

R^8 is selected from the group consisting of R^a , R^b , R^a substituted with one or more of the same or different R^a or R^b , $-OR^a$ substituted with one or more of the same or different R^a or

R^b , $-B(OR^a)_2$, $-B(NR^cR^c)_2$, $-(CH_2)_m-R^b$, $-(CHR^a)_m-R^b$, $-O-(CH_2)_m-R^b$, $-S-(CH_2)_m-R^b$,
 $-O-CHR^aR^b$, $-O-CR^a(R^b)_2$, $-O-(CHR^a)_m-R^b$, $-O-(CH_2)_m-CH[(CH_2)_mR^b]R^b$, $-S-(CHR^a)_m-R^b$,
 $-C(O)NH-(CH_2)_m-R^b$, $-C(O)NH-(CHR^a)_m-R^b$, $-O-(CH_2)_m-C(O)NH-(CH_2)_m-R^b$,
 $-S-(CH_2)_m-C(O)NH-(CH_2)_m-R^b$, $-O-(CHR^a)_m-C(O)NH-(CHR^a)_m-R^b$,
 $-S-(CHR^a)_m-C(O)NH-(CHR^a)_m-R^b$, $-NH-(CH_2)_m-R^b$, $-NH-(CHR^a)_m-R^b$, $-NH[(CH_2)_mR^b]$,
 $-N[(CH_2)_mR^b]_2$, $-NH-C(O)-NH-(CH_2)_m-R^b$, $-NH-C(O)-(CH_2)_m-CHR^bR^b$ and
 $-NH-(CH_2)_m-C(O)-NH-(CH_2)_m-R^b$;

each R^a is independently selected from the group consisting of hydrogen, (C1-C6) alkyl, (C3-C8) cycloalkyl, cyclohexyl, (C4-C11) cycloalkylalkyl, (C5-C10) aryl, phenyl, (C6-C16) arylalkyl, benzyl, 2-6 membered heteroalkyl, 3-8 membered cycloheteroalkyl, morpholinyl, piperazinyl, homopiperazinyl, piperidinyl, 4-11 membered cycloheteroalkylalkyl, 5-10 membered heteroaryl and 6-16 membered heteroarylalkyl;

each R^b is a suitable group independently selected from the group consisting of $=O$,
 $-OR^d$, (C1-C3) haloalkyloxy, $-OCF_3$, $=S$, $-SR^d$, $=NR^d$, $=NOR^d$, $-NR^cR^c$, halogen, $-CF_3$, $-CN$,
 $-NC$, $-OCN$, $-SCN$, $-NO$, $-NO_2$, $=N_2$, $-N_3$, $-S(O)R^d$, $-S(O)_2R^d$, $-S(O)_2OR^d$, $-S(O)NR^cR^c$,
 $-S(O)_2NR^cR^c$, $-OS(O)R^d$, $-OS(O)_2R^d$, $-OS(O)_2OR^d$, $-OS(O)_2NR^cR^c$, $-C(O)R^d$, $-C(O)OR^d$,
 $-C(O)NR^cR^c$, $-C(NH)NR^cR^c$, $-C(NR^a)NR^cR^c$, $-C(NOH)R^a$, $-C(NOH)NR^cR^c$, $-OC(O)R^d$,
 $-OC(O)OR^d$, $-OC(O)NR^cR^c$, $-OC(NH)NR^cR^c$, $-OC(NR^a)NR^cR^c$, $-[NHC(O)]_nR^d$,
 $-[NR^aC(O)]_nR^d$, $-[NHC(O)]_nOR^d$, $-[NR^aC(O)]_nOR^d$, $-[NHC(O)]_nNR^cR^c$, $-[NR^aC(O)]_nNR^cR^c$,
 $-[NHC(NH)]_nNR^cR^c$ and $-[NR^aC(NR^a)]_nNR^cR^c$;

each R^c is independently R^a or, alternatively, each R^c is taken together with the nitrogen atom to which it is bonded to form a 5 to 8-membered cycloheteroalkyl or heteroaryl which may optionally include one or more of the same or different additional heteroatoms and which may optionally be substituted with one or more of the same or different R^a or suitable R^b groups;

each R^d is independently R^a ;

each m is independently an integer from 1 to 3; and

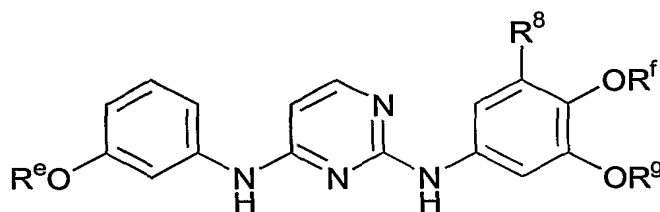
each n is independently an integer from 0 to 3, with the provisos that:

(1) when L^1 is a direct bond and R^6 is hydrogen, then R^2 is not 3,4,5-tri (C1-C6) alkoxyphenyl;

(2) when L^1 and L^2 are each direct bonds, R^2 is a substituted phenyl and R^6 is hydrogen, then R^5 is other than cyano or $-C(O)NHR$, where R is hydrogen or (C1-C6) alkyl;

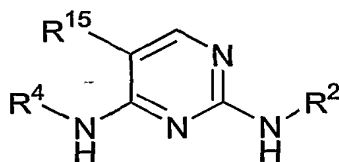
(3) when R^2 and R^4 are each independently a substituted or unsubstituted pyrrole or indole, then R^2 and R^4 are attached to the remainder of the molecule *via* a ring carbon atom; and

(4) the compound is not:



wherein: R^e is (C1-C6) alkyl; R^f and R^g are each, independently of one another a straight-chain or branched (C1-C6) alkyl which is optionally substituted with one or more of the same or different R^8 groups; and R^8 is as defined above.

46. A pharmaceutical composition comprising a pyrimidinediamine compound and a pharmaceutically acceptable carrier, diluent or excipient, said pyrimidinediamine compound being a compound according to structural formula (Id):



and salts, hydrates, solvates, N-oxides and prodrugs thereof, wherein:

R^2 and R^4 are as defined for Claim 1; and

R^{15} is an electronegative group, with the provisos that:

(1) when R^2 is 3,4,5-tri (C1-C6) alkoxyphenyl and R^{15} is halogen, then R^4 is not 3,4,5-tri (C1-C6) alkoxyphenyl; and

(2) when R^2 is a substituted phenyl, then R^{15} is other than cyano or $-C(O)NHR$, where R is hydrogen or (C1-C6) alkyl.

47. A pharmaceutical composition comprising a compound according to Claim 1 and a pharmaceutically acceptable carrier, diluent or excipient.

48. A pharmaceutical composition comprising a compound selected from any compound in TABLE 1 which inhibits mast cell or basophil cell degranulation as measured in an *in vitro* assay and a pharmaceutically acceptable carrier, diluent or excipient.

49. The composition of any one of Claims 46-48 in which the compound is in the form of a pharmaceutically acceptable salt.

50. The composition of Claim 49 in which the salt is a hydrochloride salt, a hydrogen sulfate salt, a sulfate salt, a phosphate salt, an alkane sulfonate salt, a methane sulfonate salt, an ethane sulfonate salt or a *p*-tolune sulfonate salt.

51. A method of inhibiting cell degranulation, comprising contacting a cell with an amount of a compound according to any one of Claims 1, 37 or 43 effect to inhibit degranulation.

52. The method of Claim 51 in which the cell is a human mast, basophil cell, neutrophil or eosinophil cell.

53. A method of inhibiting cell degranulation, comprising contacting a mast or basophil cell with an amount of a composition according to any one of Claims 46-48 effective to inhibit degranulation.

54. The method of Claim 53 in which the cell is a human mast, basophil cell, neutrophil or eosinophil cell.

55. A method of treating a disease characterized by, caused by or associated with mast or basophil cell degranulation, comprising administering to an animal suffering from such a disease an effective amount of a composition according to any one of Claims 46-48.

56. The method of Claim 55 in which the animal is a human.

57. The method of Claim 55 in which the disease is selected from the group consisting of allergic diseases, low grade scarring, diseases associated with tissue destruction, diseases associated with tissue inflammation, inflammation, and scarring.

58. The method of Claim 57 in which the allergic disease is selected from the group consisting of conjunctivitis, rhinitis, asthma, atopic dermatitis and food allergies.

59. The method of Claim 57 in which the low grade scarring is selected from the group consisting of scleroderma, increased fibrosis, keloids, post-surgical scars, pulmonary fibrosis, vascular spasms, migraine, reperfusion injury and post myocardial infarction.

60. The method of Claim 57 in which the disease associated with tissue destruction is selected from the group consisting of COPD, cardiobronchitis and post myocardial infarction.

61. The method of Claim 57 in which the disease associated with tissue inflammation is selected from the group consisting of irritable bowel, spastic colon and inflammatory colon disease.

62. A method of inhibiting a Syk kinase, comprising the step of contacting the Syk kinase or an active fragment thereof with an effective amount of a 2,4-pyrimidinediamine compound according to Claim 1.

63. The method of Claim 62 which is practiced *in vitro* with an isolated or recombinant Syk kinase.

64. The method of Claim 62 in which the Syk kinase is practiced *in vitro* with a cell or cell population that expresses an endogenous or recombinant Syk kinase.

65. The method of Claim 62 which is practiced *in vivo*.

66. A method of inhibiting a Syk kinase in an animal, comprising the step of administering to the animal an amount of a 2,4-pyrimidinediamine compound according to Claim 1 effective to inhibit the Syk kinase.

67. A method of treating or preventing a disease mediated at least in part by Syk kinase activity, comprising the step of administering to an animal in need thereof an amount of a 2,4-pyrimidinediamine compound according to Claim 1 effective to inhibit the Syk kinase activity, thereby treating or preventing the disease.

68. A method of treating or preventing a disease mediated at least in part by Syk kinase activity, comprising the step of administering to an animal in need thereof an amount of a composition according to Claim 46 effective to inhibit the Syk kinase activity, thereby treating or preventing the disease.

69. The method of Claim 72 or 74 in which the animal is a human.

70. A method of inhibiting an Fc receptor signal transduction cascade, contacting a cell comprising an Fc receptor having a gamma homodimer with an amount of a 2,4-pyrimidinediamine compound according to Claim 1 effective to inhibit its signal transduction cascade.

71. The method of Claim 70 in which the Fc receptor is selected from the group consisting of Fc α RI, FC γ RI, FC γ RIII and Fc ϵ RI.

FIG. 1

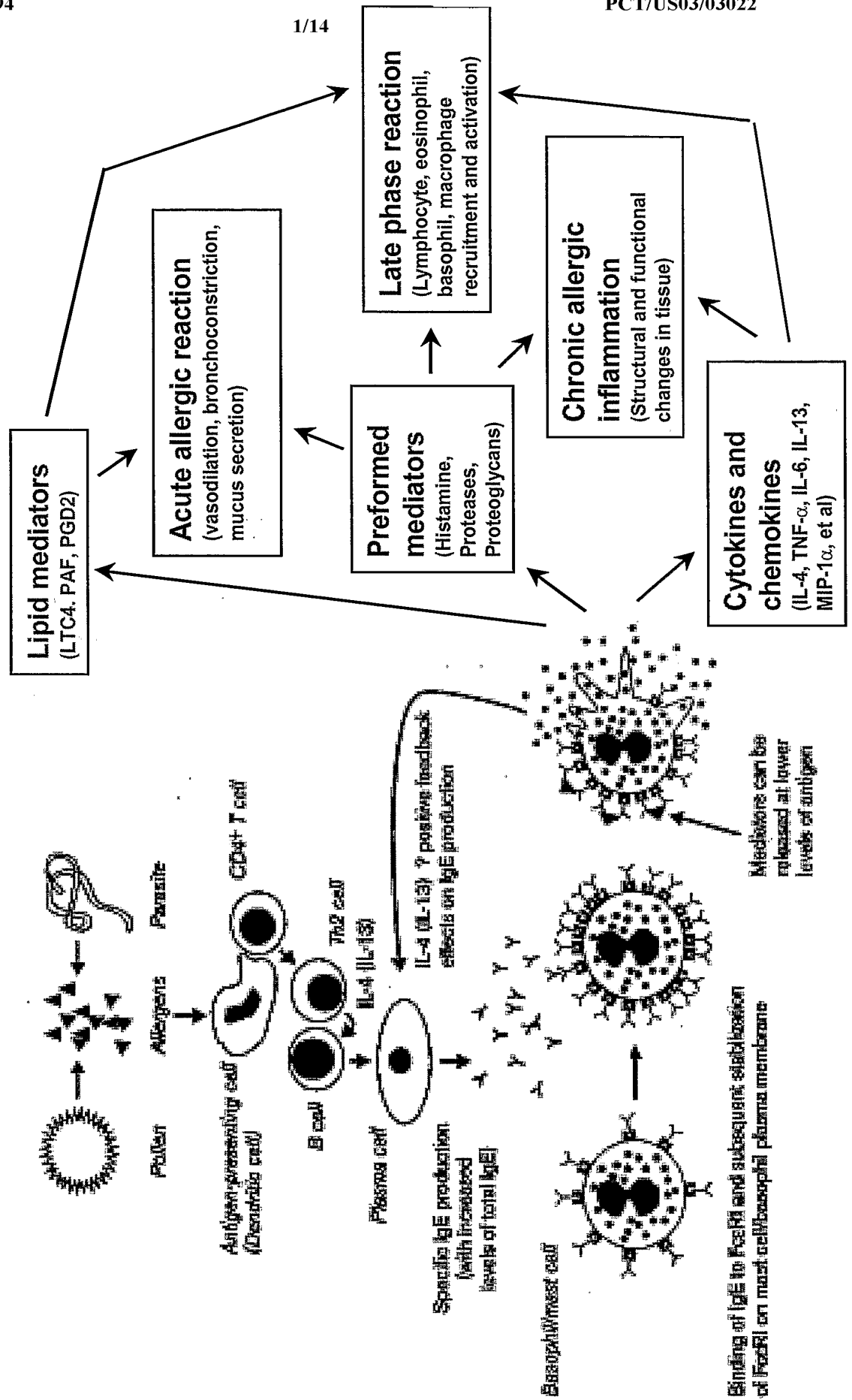


FIG. 2
Mast Cell FcεR1 Signaling Pathway

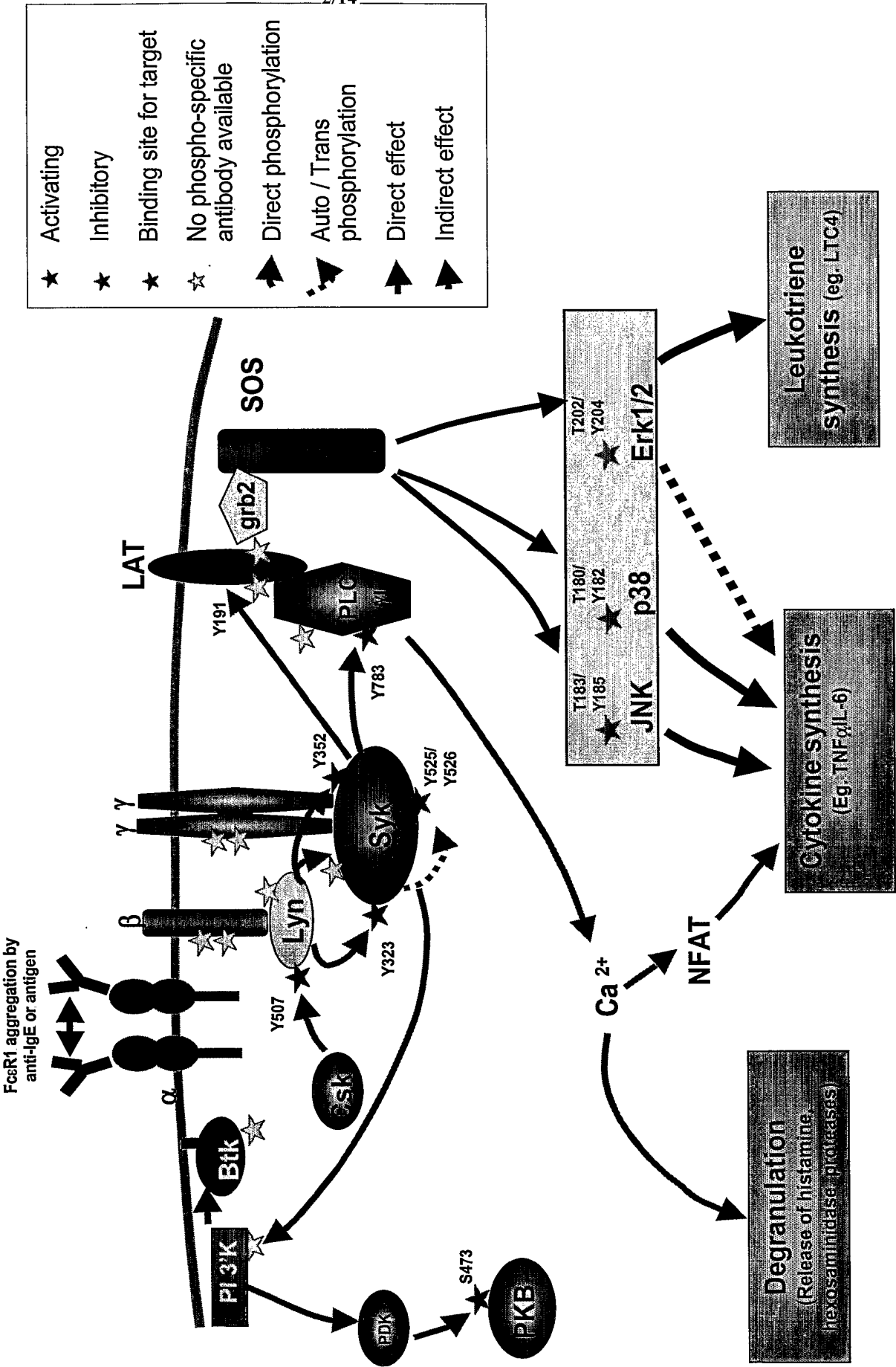
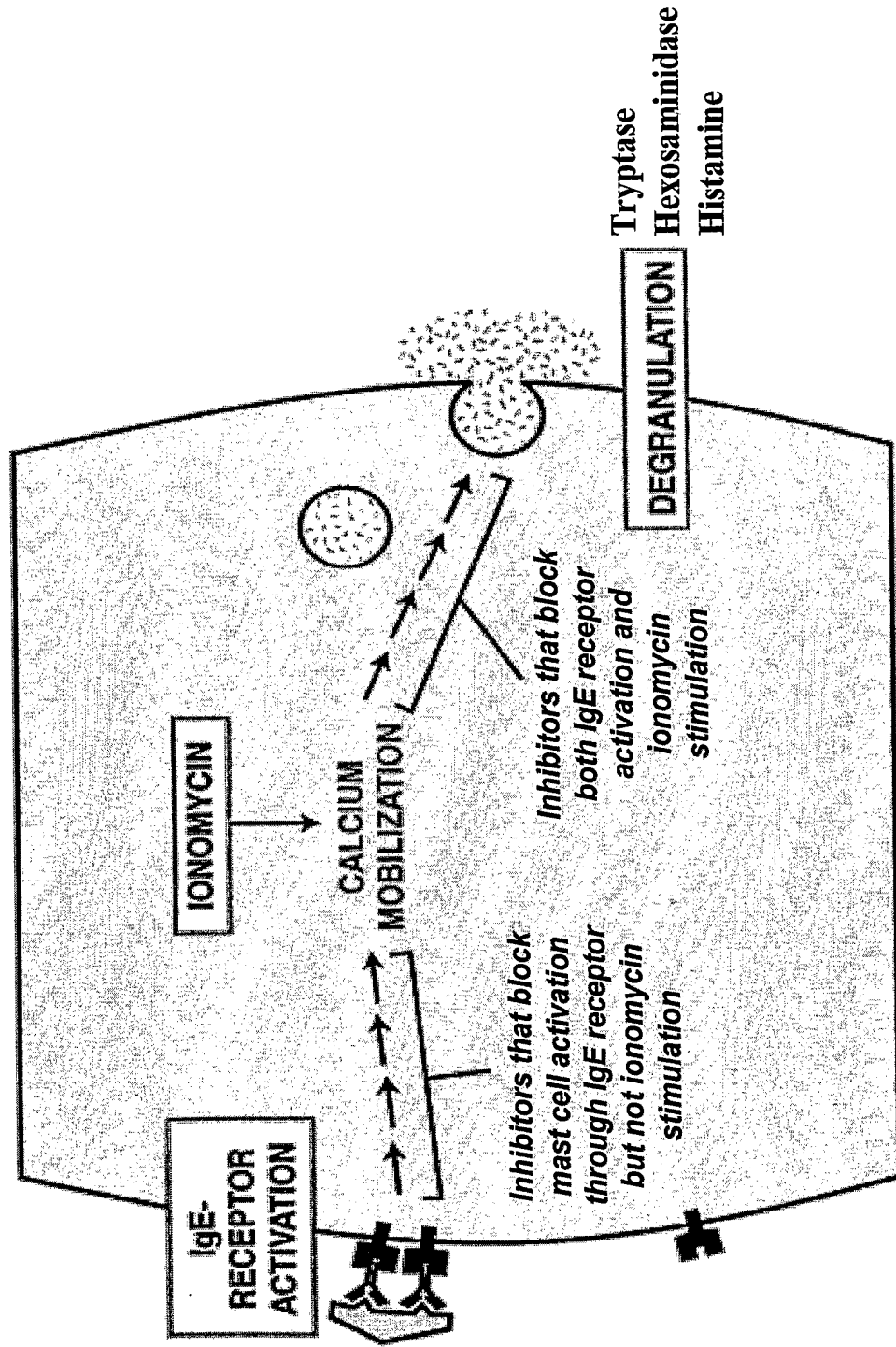


FIG. 3



Crosslinking of IgE
with anti-IgE antibody

FIG. 4

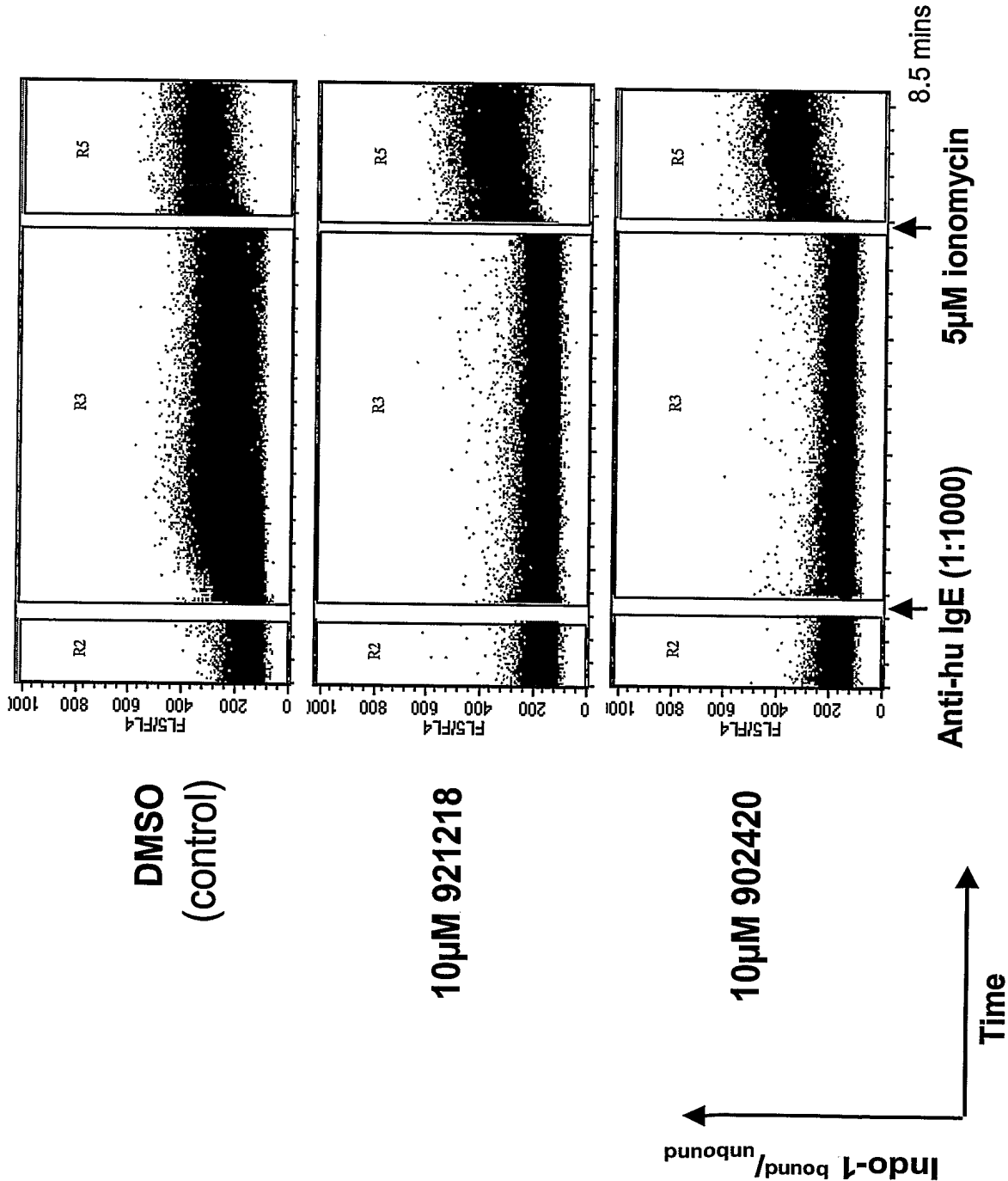


FIG. 5

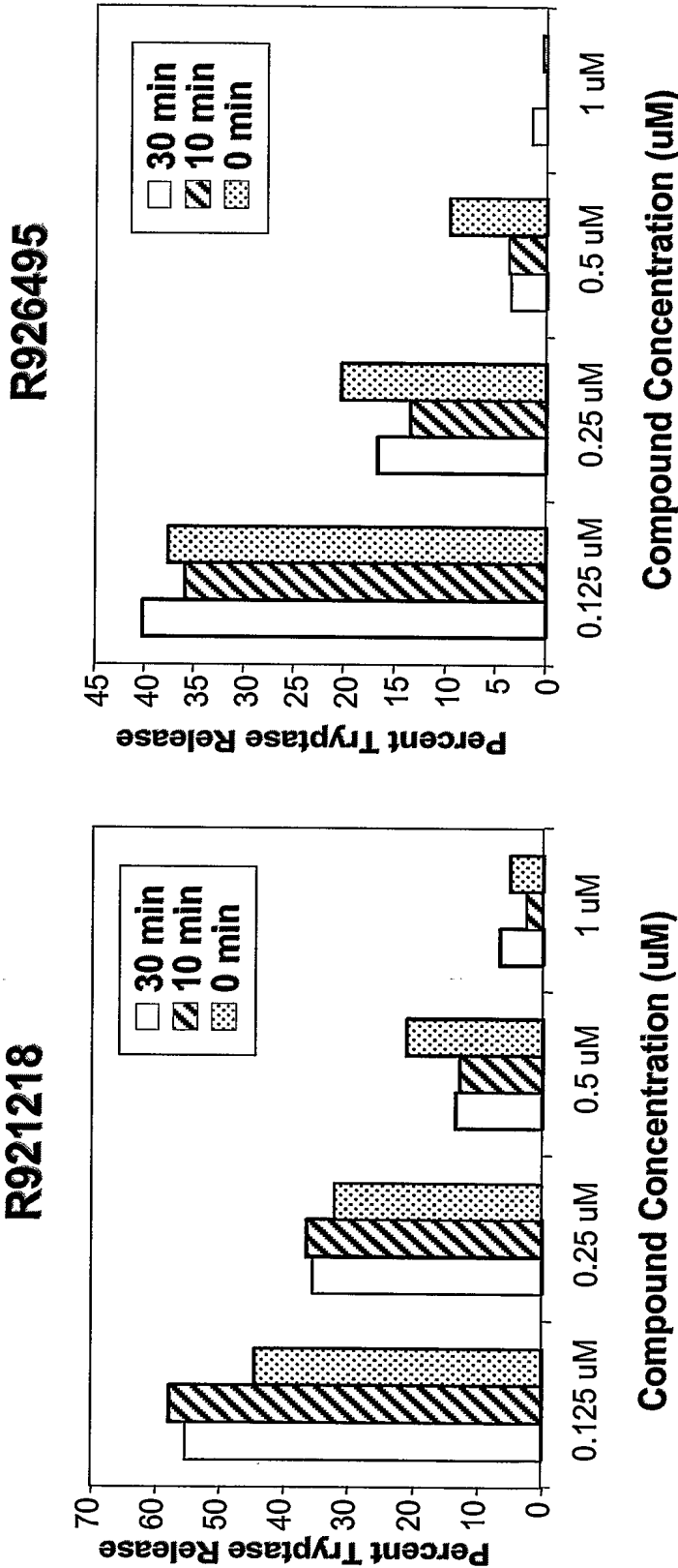


FIG. 6

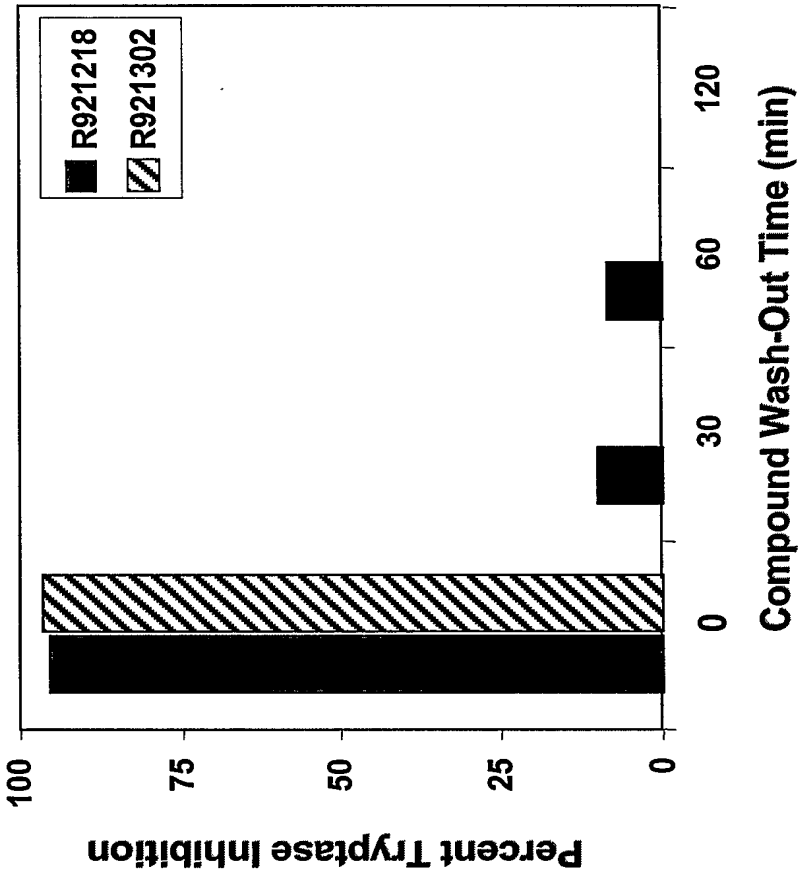


FIG. 7

Inhibition of Phosphorylation of Proteins Downstream of
Syk Kinase in Fce Receptor Activated BMMC Cells

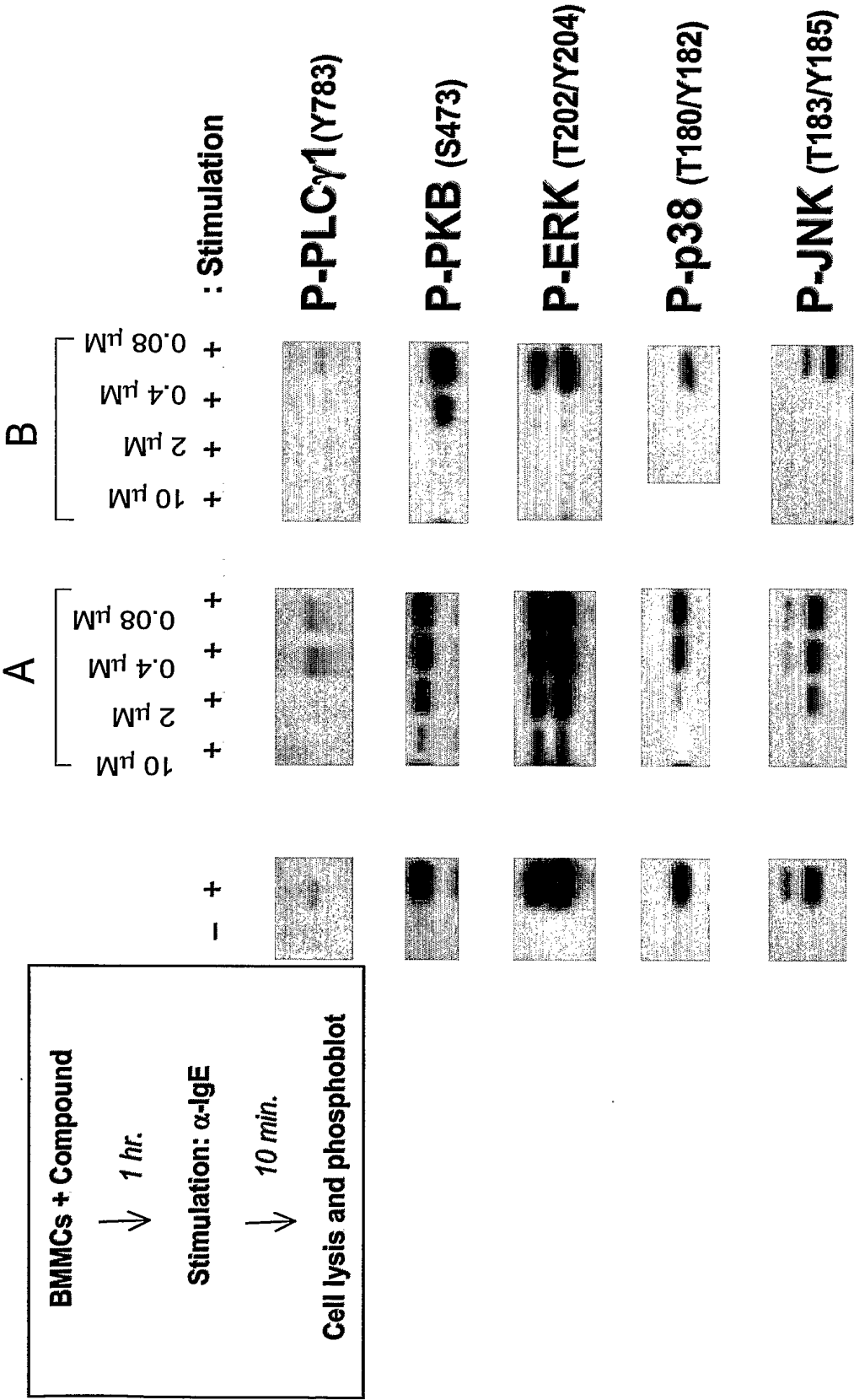
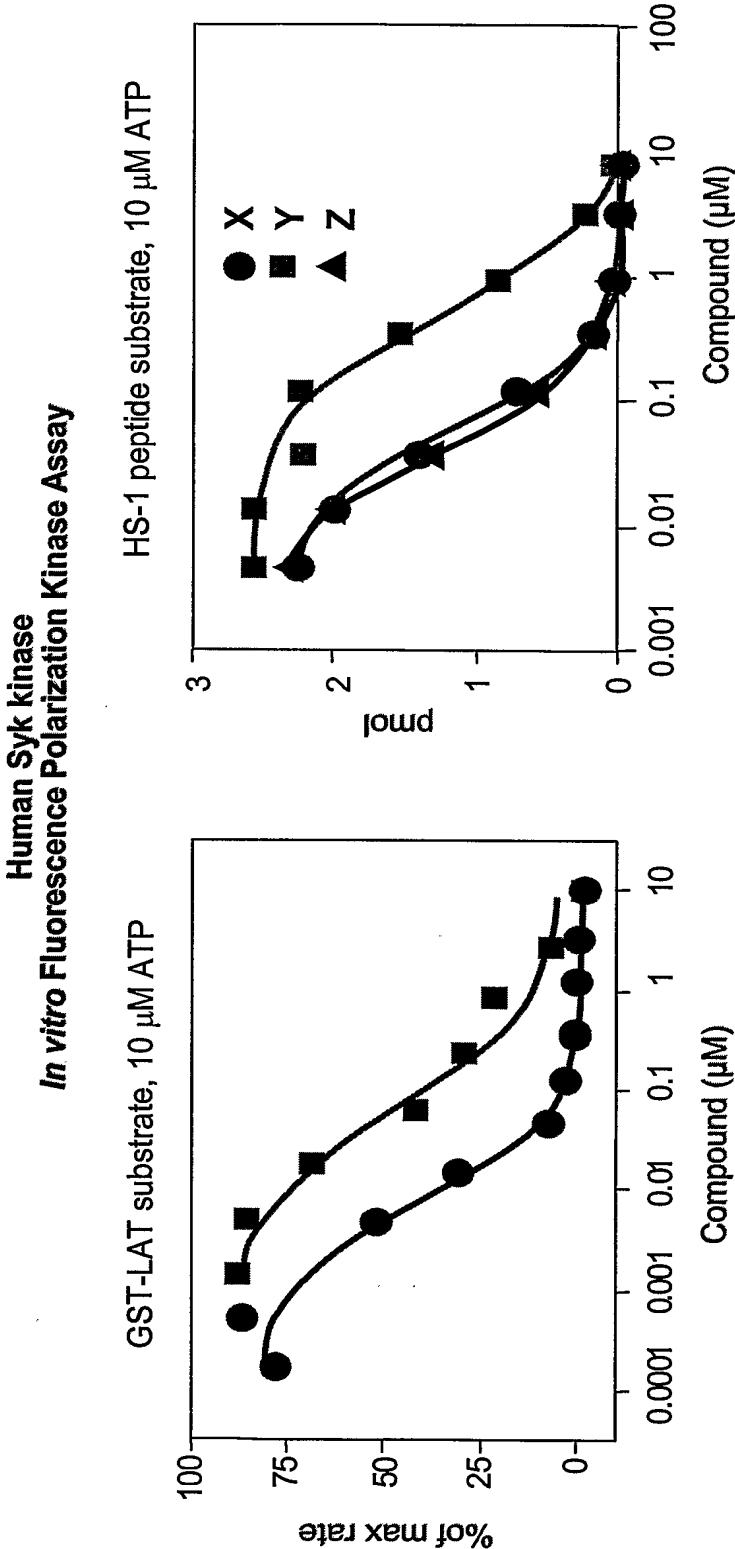


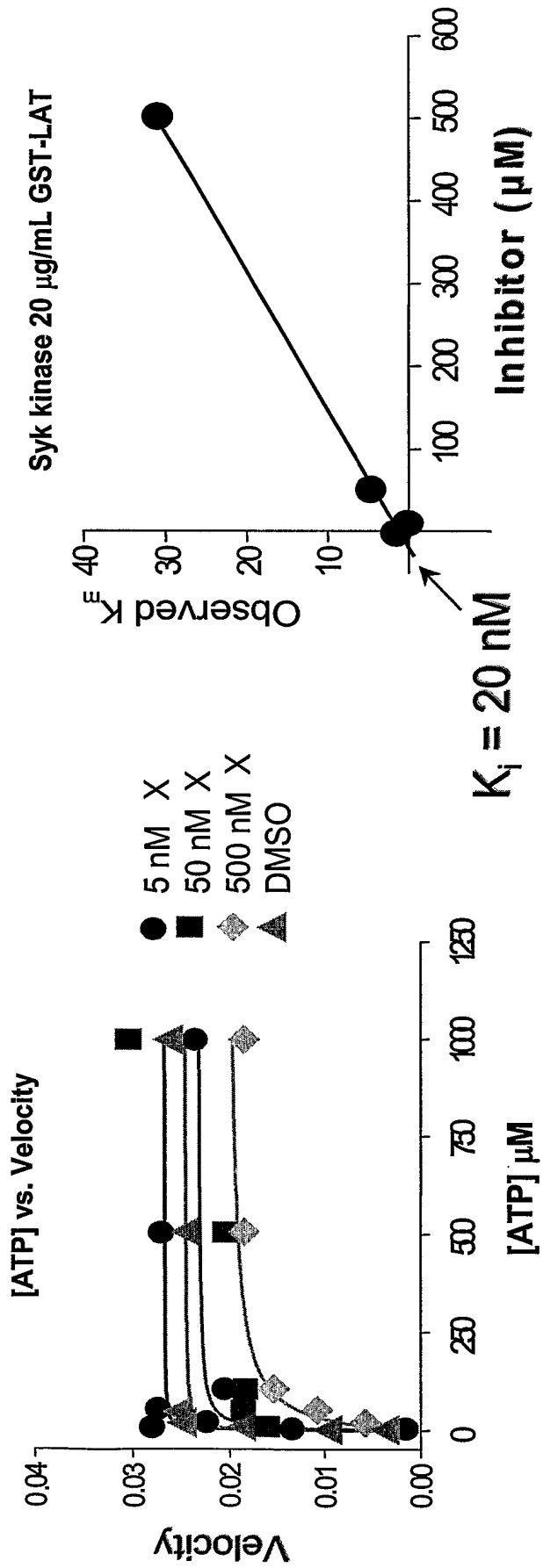
FIG. 8

The Disclosed Compounds Potently Inhibit the Activity of Syk Kinase



| IC ₅₀ (nM) | |
|-----------------------|------|
| GST-LAT | HS-1 |
| Y | 200 |
| X | 10 |
| Z | 62 |
| | ND |
| | 43 |

FIG. 9
Compound Inhibition of Syk is ATP Competitive



| | | | | |
|-----------|------|--------|---------|----------|
| | DMSO | 5 nM X | 50 nM X | 500 nM X |
| V_{max} | .025 | 0.027 | .023 | 0.020 |
| K_m | 1.54 | 0.79 | 4.5 | 31 |

FIG. 10

CHMC: Cultured human mast cells

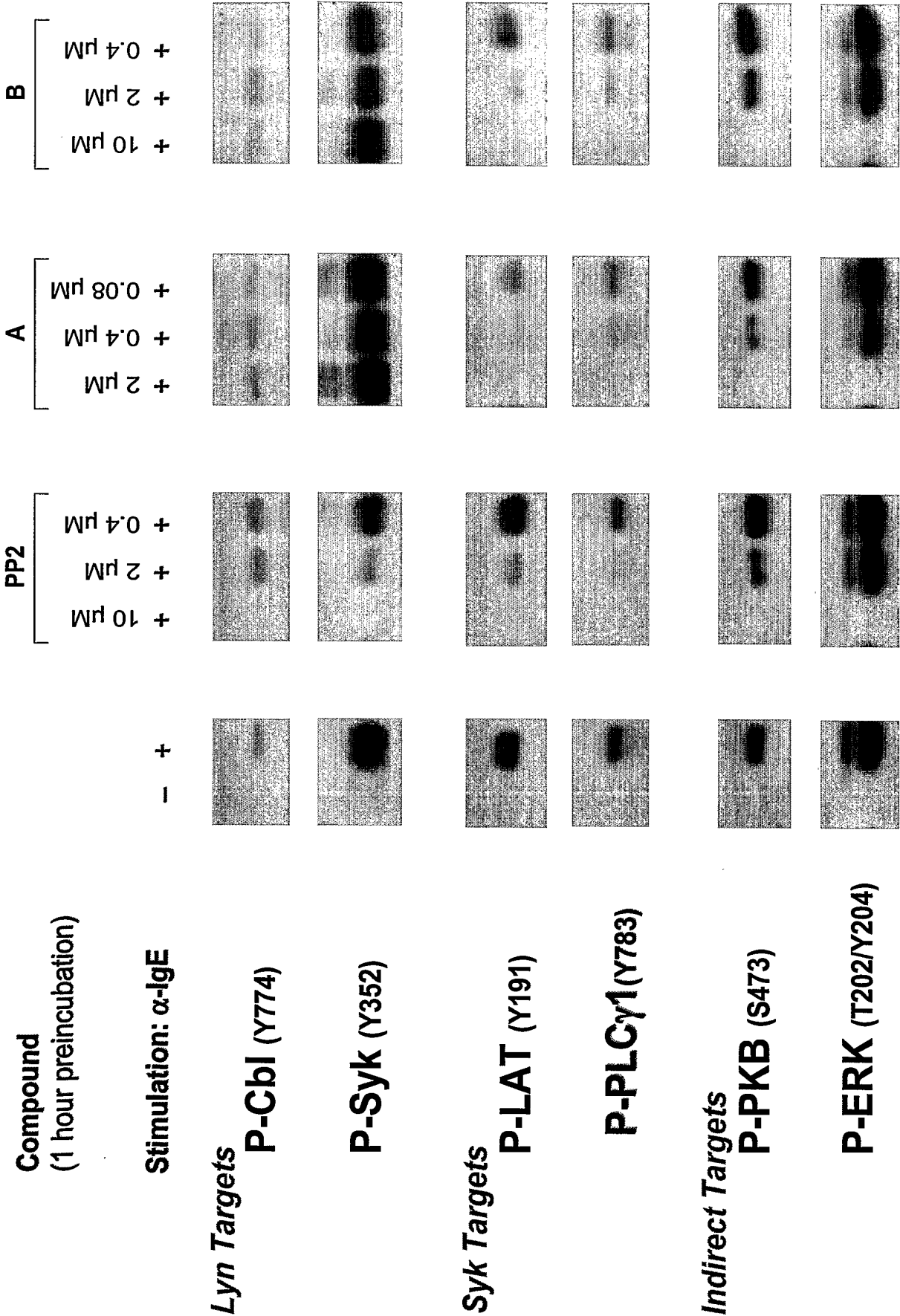


FIG. 11A
Inhibition of Phosphorylation of Proteins downstream of Syk in BMMC

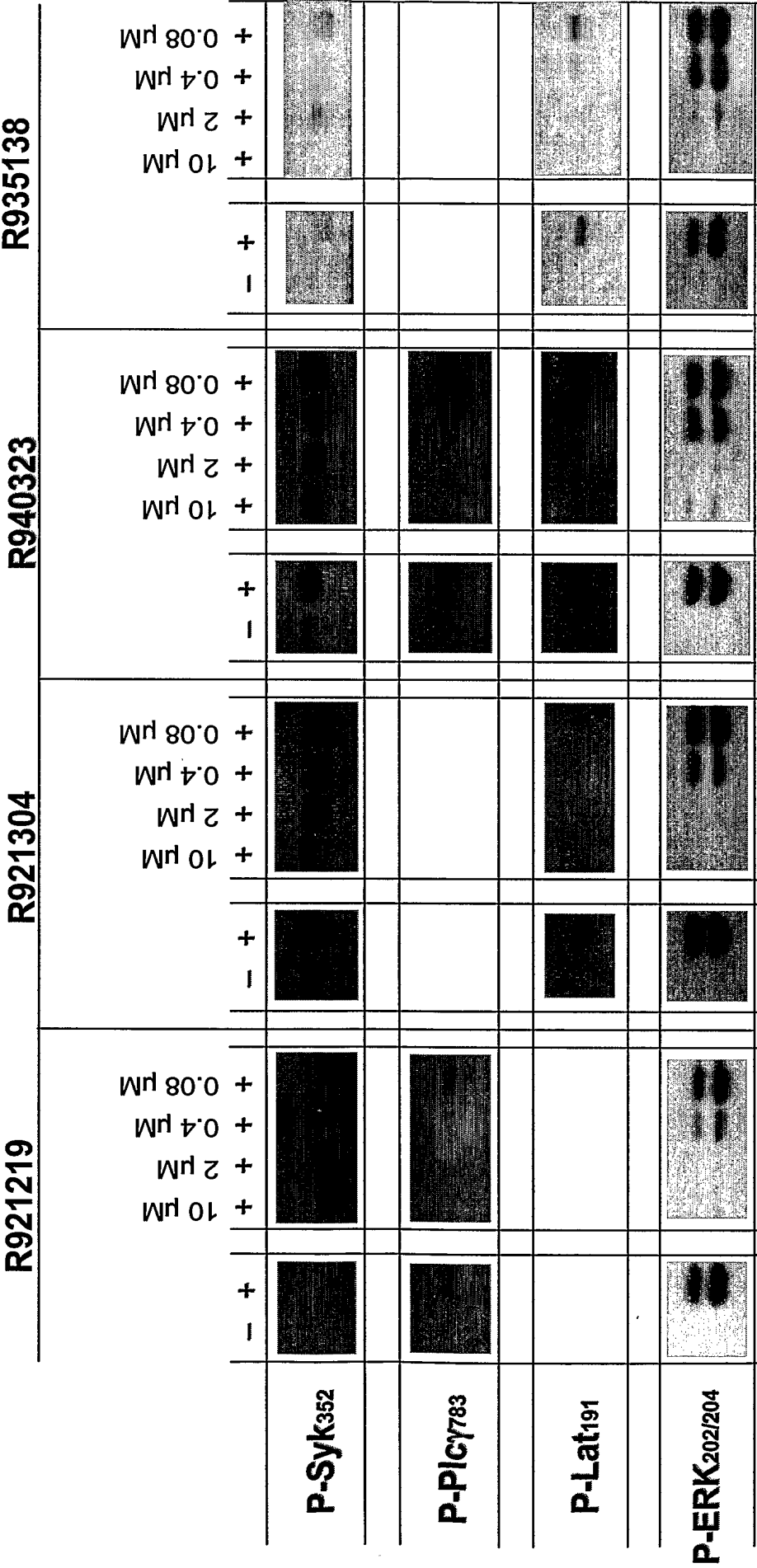


FIG. 11B

Inhibition of Phosphorylation of Proteins downstream of Syk in BMMC

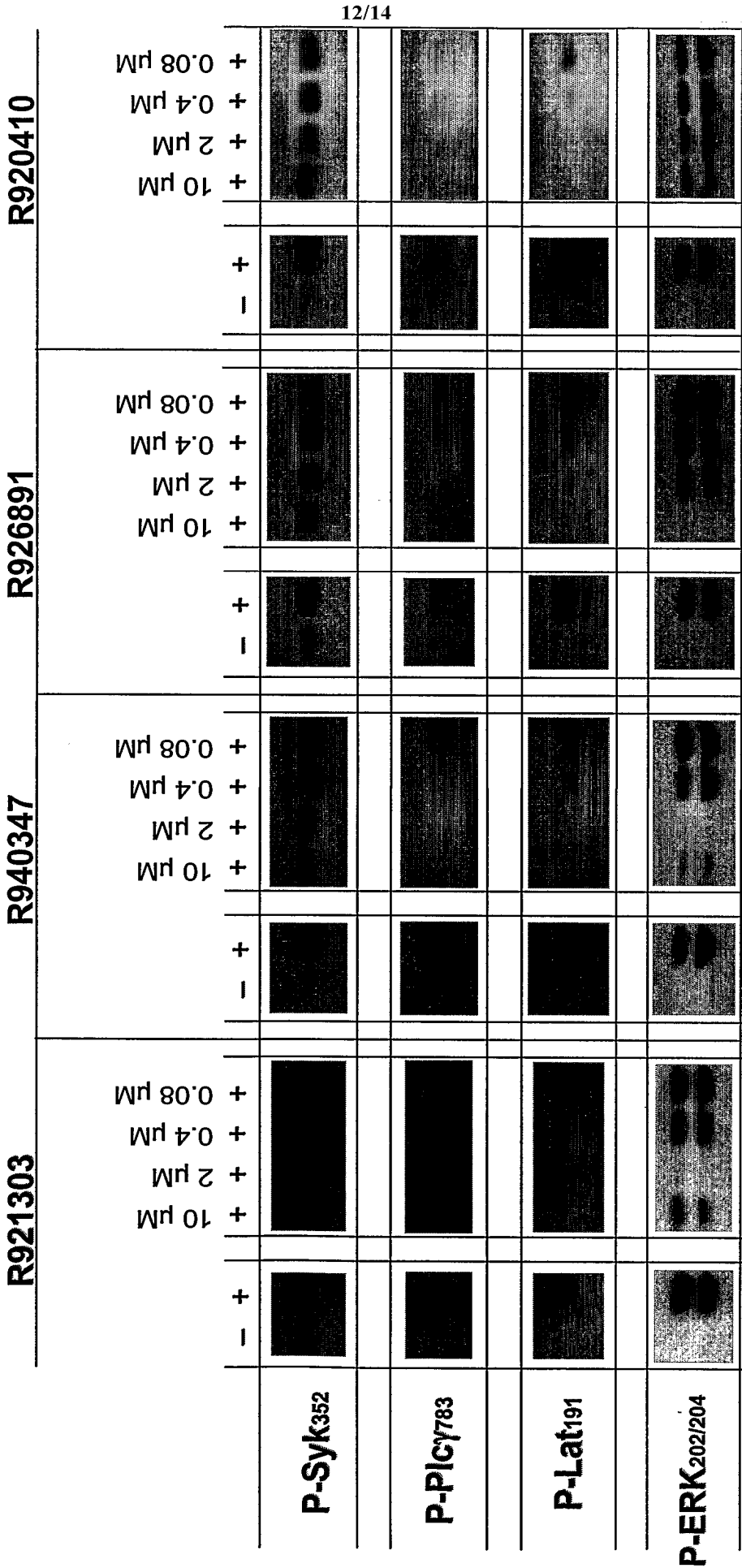


FIG. 11C
Inhibition of Phosphorylation of Proteins downstream of Syk in BMBC

| R926321 | | | | R950368 | | | | R926594 | | | | R935310 | | | |
|-------------------------------|---|---|--------------|-------------|---------------|----------------|--|---------|---|---|--------------|-------------|---------------|----------------|--|
| | + | - | + 10 μ M | + 2 μ M | + 0.4 μ M | + 0.08 μ M | | | + | - | + 10 μ M | + 2 μ M | + 0.4 μ M | + 0.08 μ M | |
| P-Syk ₃₅₂ | | | | | | | | | | | | | | | |
| P-Plc γ ₇₈₃ | | | | | | | | | | | | | | | |
| P-Lat ₁₉₁ | | | | | | | | | | | | | | | |
| P-ERK _{202/204} | | | | | | | | | | | | | | | |

FIG. 11D
Inhibition of Phosphorylation of Proteins downstream of Syk in BMMC

| | R935237 | | | | | | R926813 | | | | | | R926839 | | | | | | R908712 | | | | | |
|-------------------------------|---------|---|------------|-----------|-------------|----------------|---------|---|------------|-----------|-------------|----------------|---------|---|------------|-----------|-------------|----------------|---------|---|------------|-----------|-------------|----------------|
| | - | + | 10 μ M | 2 μ M | 0.4 μ M | + 0.08 μ M | - | + | 10 μ M | 2 μ M | 0.4 μ M | + 0.08 μ M | - | + | 10 μ M | 2 μ M | 0.4 μ M | + 0.08 μ M | - | + | 10 μ M | 2 μ M | 0.4 μ M | + 0.08 μ M |
| P-Syk ₃₅₂ | | | | | | | | | | | | | | | | | | | | | | | | |
| P-Plc γ ₇₈₃ | | | | | | | | | | | | | | | | | | | | | | | | |
| P-Lat ₁₉₁ | | | | | | | | | | | | | | | | | | | | | | | | |
| P-ERK _{202/204} | | | | | | | | | | | | | | | | | | | | | | | | |